NQ Update
Chronic Disease Theme

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HOT NORTH SEMINAR, Broome

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CENTRE FOR CHRONIC DISEASE PREVENTION

New paradigm in understanding of many chronic diseases

- Common inflammatory pathways and co-evolution and interplay of the metabolic/immune systems in the context of obesity
- Key role of the microbiota and nutrition in human health

- Epigenetic upregulation, especially important in generational amplification of T2DM, CVD risk

- Understanding “social determinants” as biological pathways – concept of “allostatic load” including psychosocial stress pathways

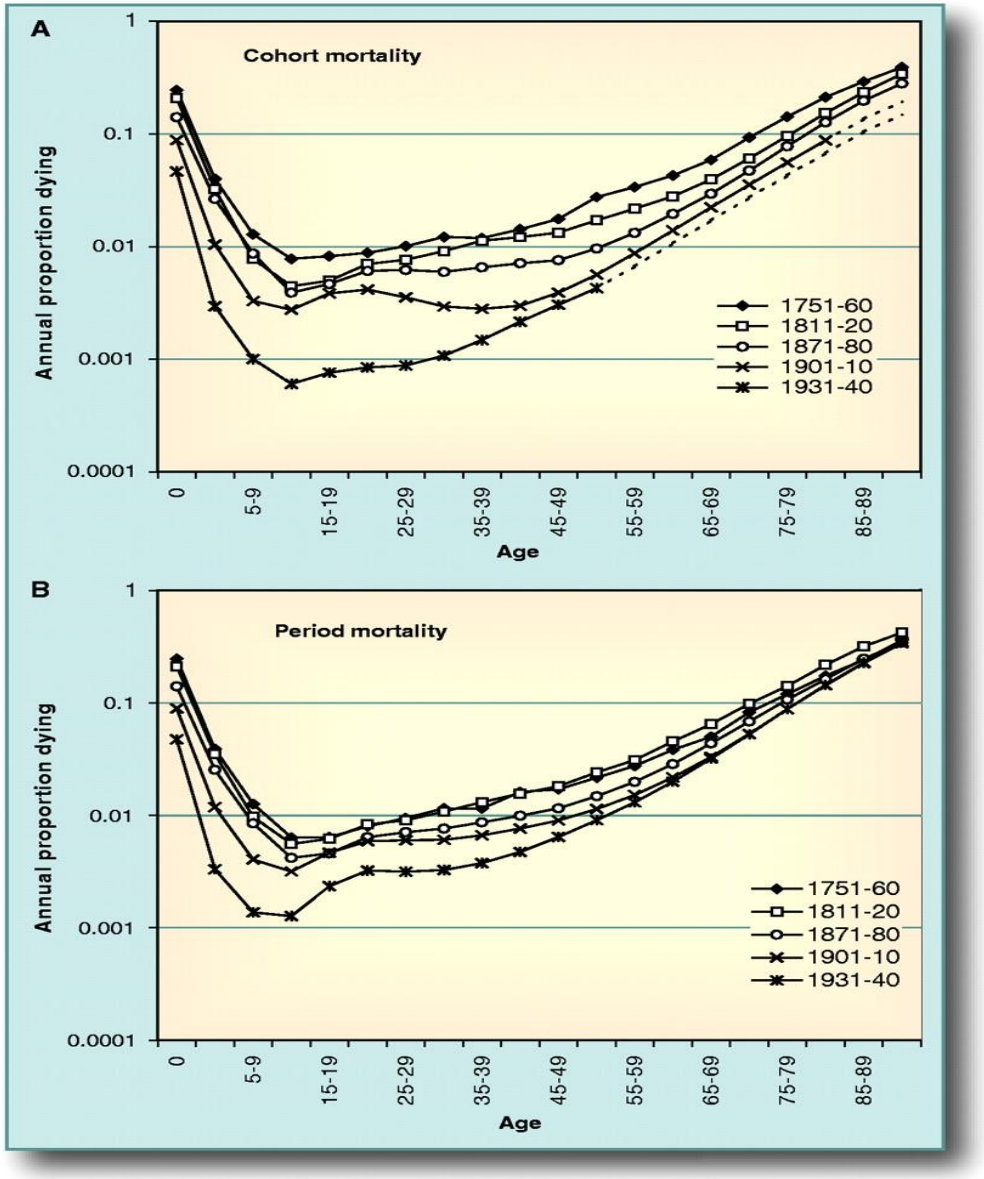
Today

- Chronic inflammation as a common pathway in chronic disease
- New tools: Whole genome sequencing, advanced analytical methods, simpler field collection and analytical methods (PUFA) – combine metabolic, nutritional, inflammatory cytokines and gut microbiota measures (human microbiome project)
- Old friends: “Parasites” and real food in high risk transitional populations in northern Australia and the region
- Insights from some work in progress in northern Australia

Insights from the historical records: Inflammatory exposure and cohort changes in human life-spans

- Increased life expectancy at older ages over history emphasized public health and nutrition improvements
- Analysis of birth cohorts in Sweden since 1751 shows a strong cohort effect at all ages – early-age mortality predicts old-age mortality
- Does a “cohort morbidity phenotype” (enduring effects of early environment, especially infections) represent ***inflammatory processes that persist from early age to adult life?***

Age-specific mortality over the life-span, Sweden, 1751 to 1940 (semi-log scale)



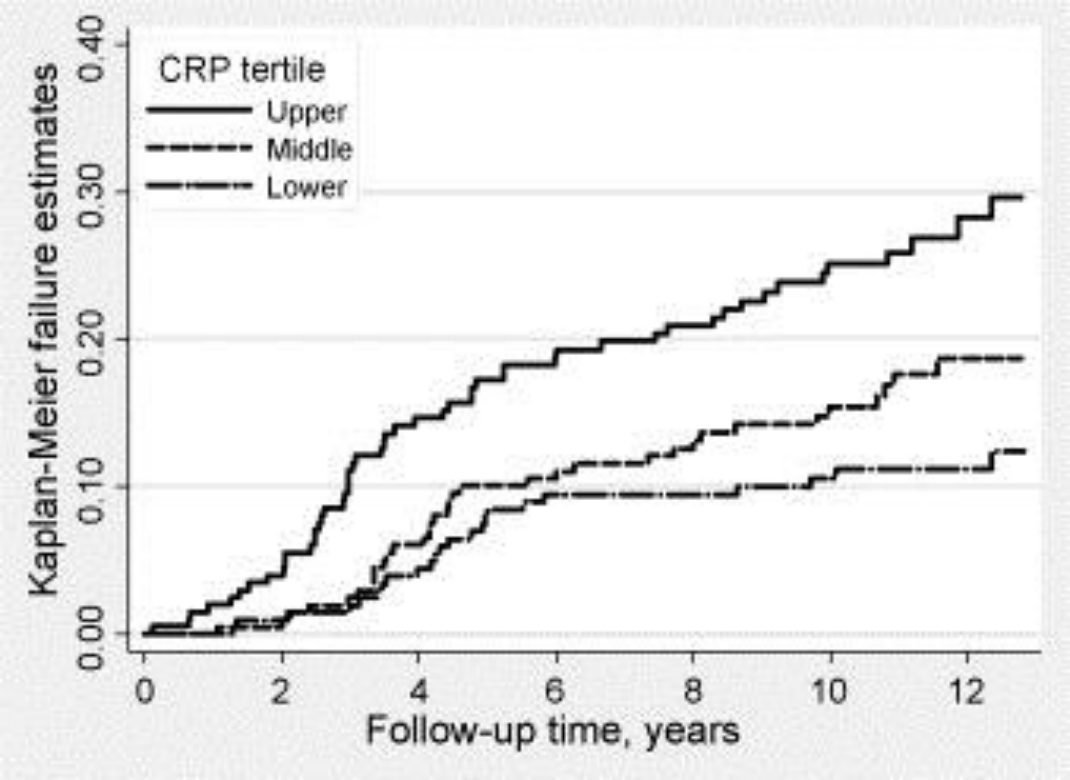
Caleb E. Finch, and Eileen M. Crimmins Science 2004;305:1736-1739

The importance of early life exposures

- The historical mortality decline among the old and the young begins in the same cohort
- Most of the variance in this series was explained by mortality before the age of 10
- Infant mortality has a stronger relationship to older-age mortality than does mortality in subsequent childhood years
- The annualised effect of each childhood year on old-age mortality is ***3 times greater for infancy*** than subsequent childhood years

Chronic inflammation

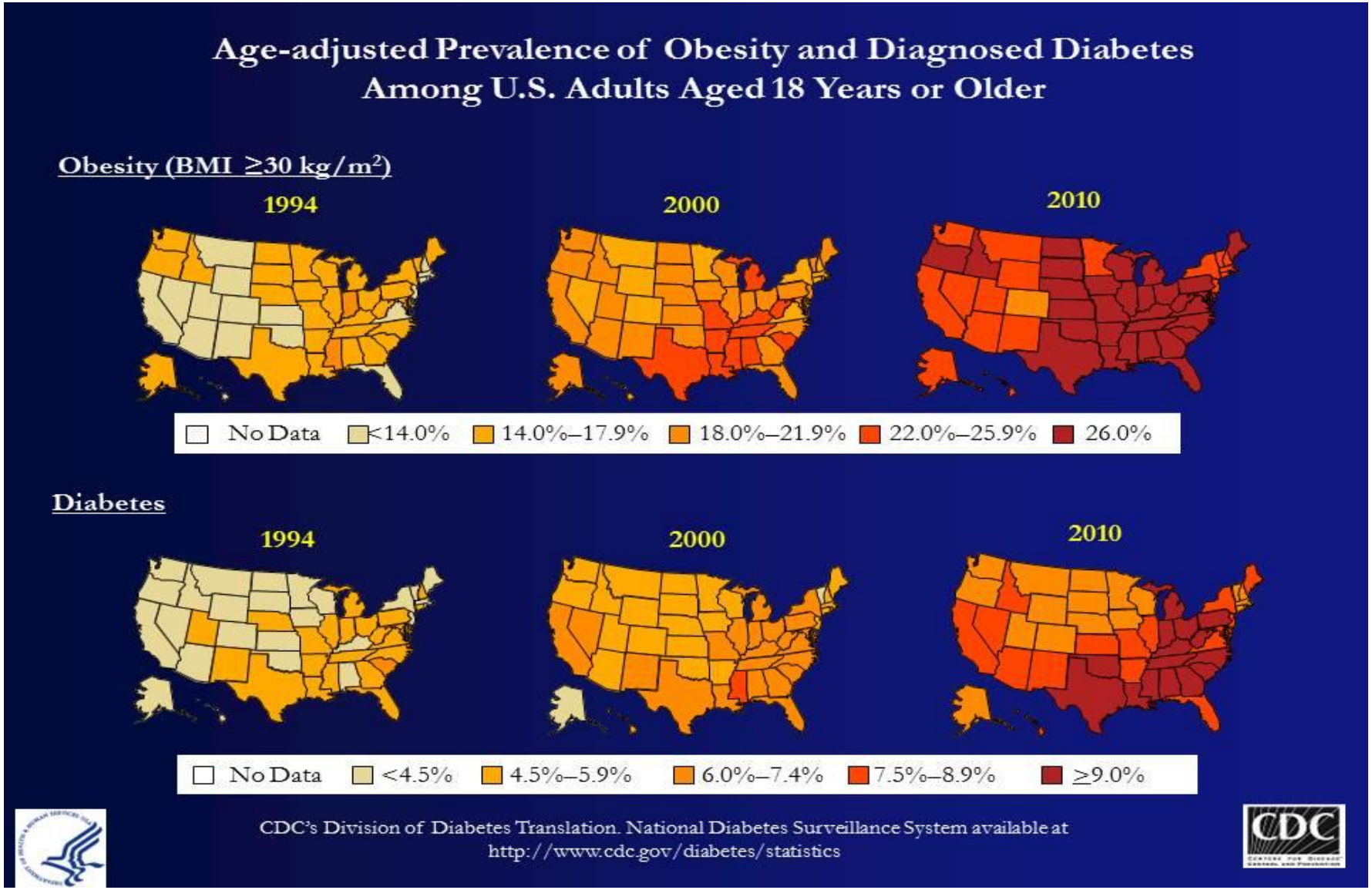
C-reactive protein and the risk of developing type 2 diabetes in Aboriginal Australians



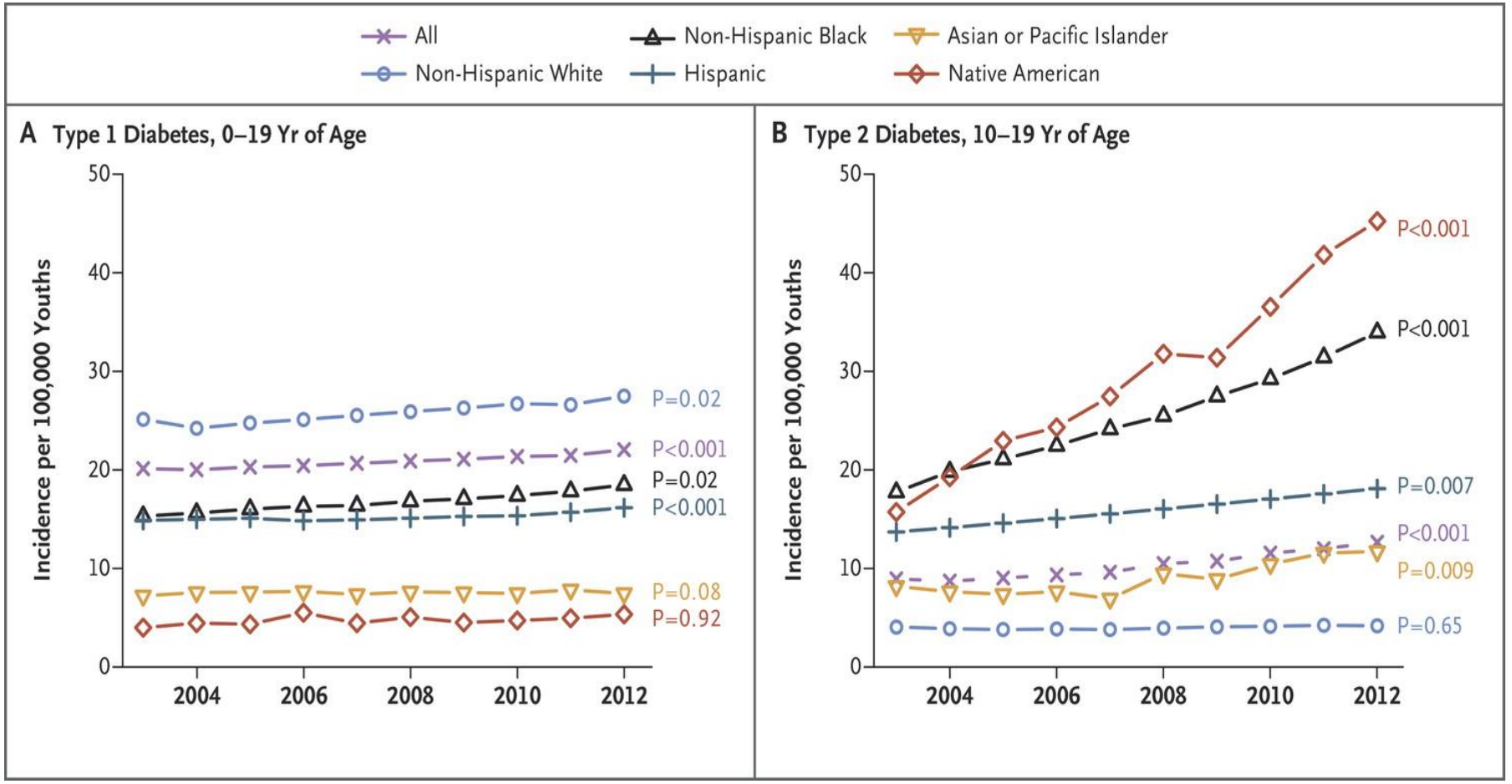
Kaplan–Meier estimates of the cumulative distribution function for developing type 2 diabetes during the follow-up period in Aboriginal Australians.

Source: Zhiqiang Wang, Wendy E. Hoy Diabetes Research and Clinical Practice, Volume 76, Issue 1, 2007, 37–43 http://dx.doi.org/10.1016/j.diabres.2006.07.018

Diabesity in the USA



Model-Adjusted Diabetes Incidence Estimates in Children, USA.



Mayer-Davis EJ et al. N Engl J Med 2017;376:1419-1429.

A 5-year-old girl with type 2 diabetes

Dev Kevat, Dyanne Wilson, Ashim Sinha

Lancet 2014; 383: 1268

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In August, 2013, a 5-year-old Indigenous girl accompanied her mother to her diabetes outreach appointment in a remote community in Australia. Towards the end of her consultation, the mother mentioned concerns about non-healing sores on her daughter's thighs. Noting the child's obesity, two random blood glucose level tests were done, showing concentrations of 19·2 mmol/L and 18·7 mmol/L. A urine dipstick test was negative for ketones. The girl's mother reported that the sores had been present for roughly 5 weeks, and bedwetting for the past 12 months. There was no history of diarrhoea or vomiting. The child was born macrosomic (4·5 kg) at 38 weeks by caesarean section after a pregnancy complicated by poorly controlled gestational diabetes. Her diet was high in large portions of refined carbohydrates and simple sugars. There was a strong family history of type 2 diabetes.

The patient was above the 95th centile for weight (36 kg), body-mass index (24·5 kg/m²) and height (123 cm). Crusted sores on both upper thighs and right axilla were consistent with impetigo. The rest of the examination was unremarkable except for acanthosis nigricans in the axillae and around the neck (figure). The patient had high concentrations of HbA_{1c} (11·9%, normal range 4·3–6·0; or 107 mmol/mol, 23–42), plasma glucose (19·5 mmol/L, 3·0–7·8), C-peptide (1·6 mmol/L, 0·3–1·4), and insulin (201 pmol/L, 14–160). Urine albumin:creatinine ratio was normal (0·3 g/mol creatinine, normal <1·0). Tests for type 1 diabetes autoantibodies and genetic tests for *MODY1* (*HNF4A*) and *MODY3* (*HNF1A*) were negative. The patient was transferred to a tertiary centre and given intravenous antibiotics for infection, and metformin and insulin for type 2 diabetes. When seen for follow-up in November, 2013, she was no longer taking metformin because of intolerance, but remained on insulin. Blood glucose concentrations remained above target levels at 10–13 mmol/L.

Driven by increased urbanisation, high calorie diets, and increasingly sedentary lifestyles, the worldwide rise in the incidence of type 2 diabetes has predominantly occurred in adults. However, children are also being affected.[1] The continued burden of infectious diseases (eg, respiratory and diarrhoeal illnesses) coupled with an increasing prevalence of chronic diseases (particularly cardiovascular disease and type 2 diabetes) has resulted in Indigenous Australians having an additional 70% disease burden compared with the general Australian population.[2] Remote Indigenous communities are generally socioeconomically poor yet pay high prices for fresh food because of transport costs and limited competition. In addition to adverse socioeconomic determinants, genetic factors and in-utero exposure to hyperglycaemia[3] probably contributed to this child's risk of developing type 2 diabetes. The US SEARCH study[4] provides epidemiological data about the incidence of diabetes in young people. In our experience with this population, compliance and good diabetic control is often difficult to achieve and sustain—the TODAY trial[5] showed that even under trial conditions 52% of children on metformin alone, and 39% of children on combination oral treatment lost glycaemic control (HbA_{1c} >8% for 6 months or required insulin), over an average follow-up period of 3·9 years. Further long-term outcome studies are needed to determine the most efficacious combinations of interventions for type 2 diabetes in children who have extra decades to accrue disabling complications.

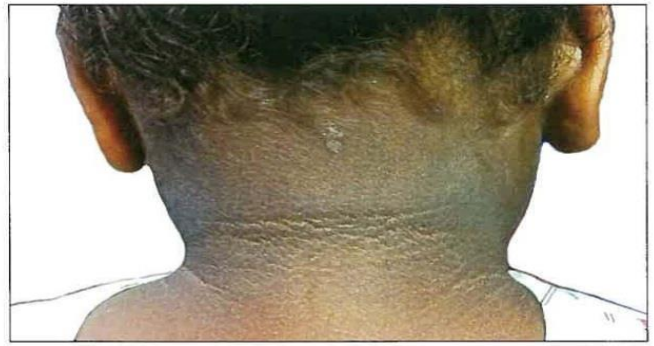


Figure: Acanthosis nigricans

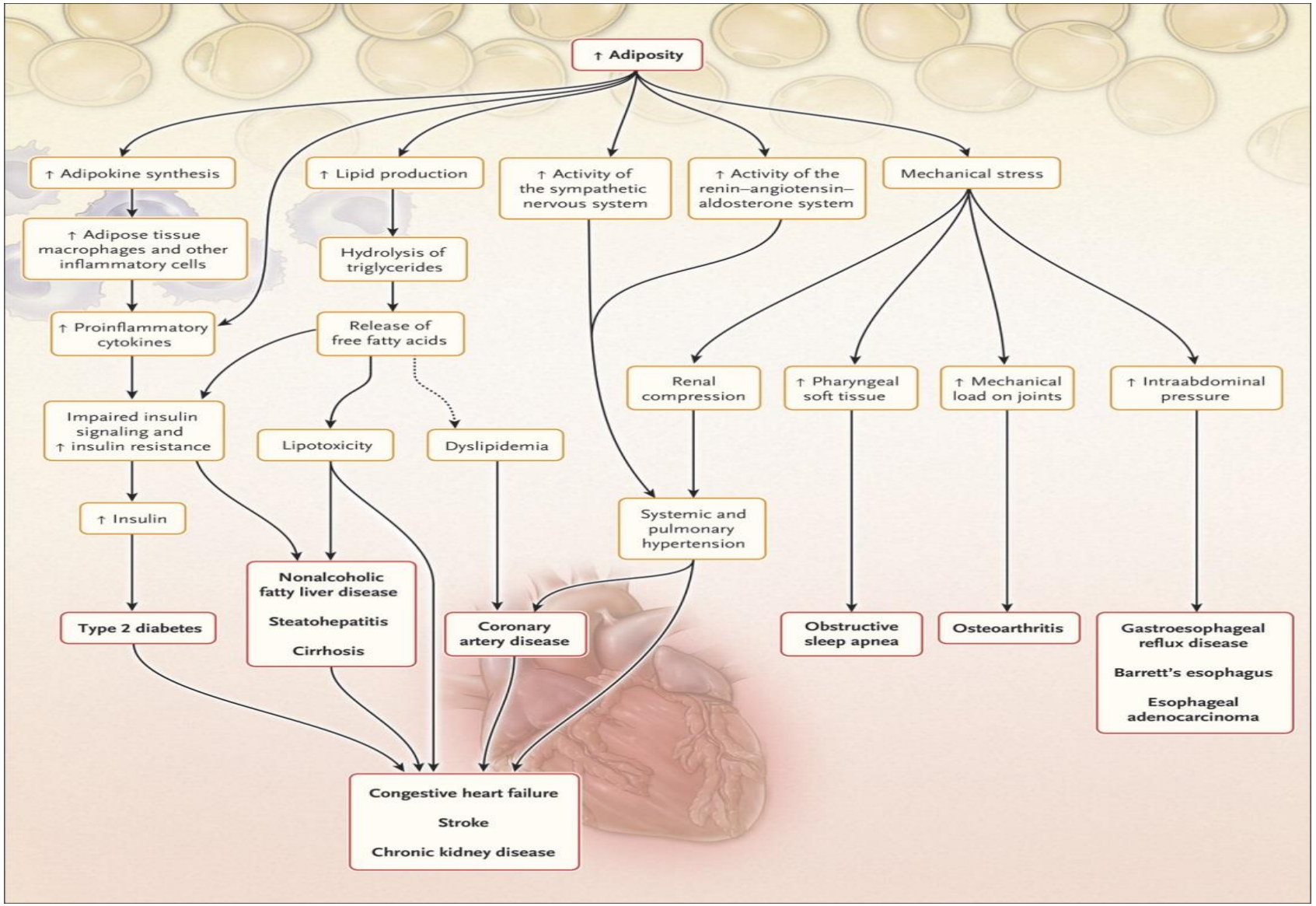
Contributors
DK wrote the report and initially managed the patient. DW and AS helped revise the report and assisted with references, and have provided ongoing care to the patient. Written consent to publish was obtained.

Declaration of interests
AS has been on advisory boards for Sanofi-Aventis and AstraZeneca-BMS; been on speakers bureaux for Eli Lilly, AstraZeneca-BMS, Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme, Takeda, Servier, and Novartis; and received research grants from Novo Nordisk and Merck. DK and DW declare that they have no competing interests.

References

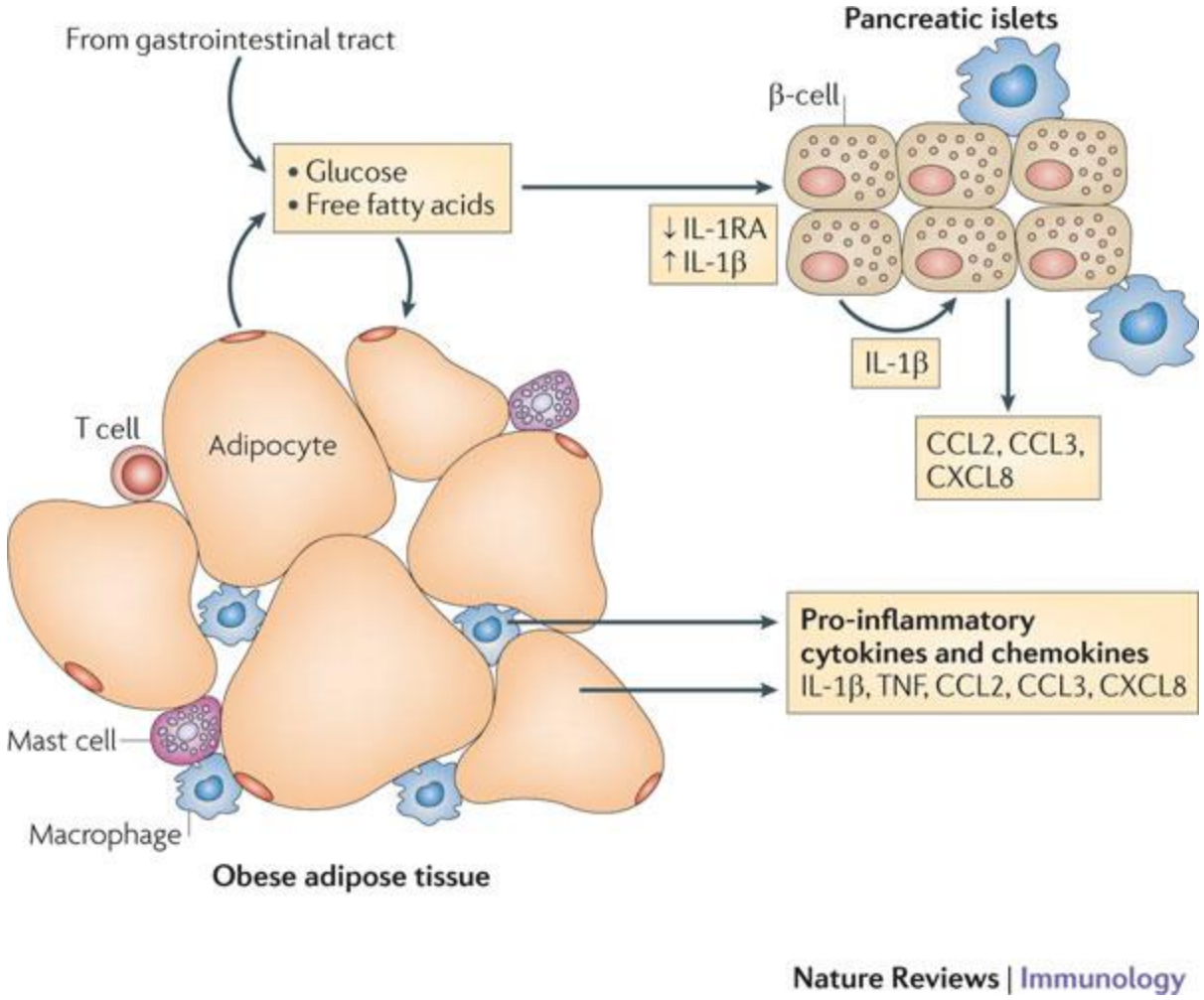
1 Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes in children and adolescents. *J Paediatr* 2005; **146:** 693–700.
2 Vos T, Barker B, Begg S, Stanley L, Lopez A. Burden of disease and injury in Aboriginal and Torres Strait Islander Peoples: the Indigenous health gap. *Int J Epidemiol* 2009; **38:** 470–77.
3 Dabelea D, Hanson R, Lindsay R, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000; **49:** 2208–11.
4 The Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. *JAMA* 2007; **297:** 2716–24.
5 TODAY Study Group. Clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; **366:** 2247–56.

Current Understanding of Pathways through Which Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases.



Heymsfield SB, Wadden TA. N Engl J Med 2017;376:254-266.

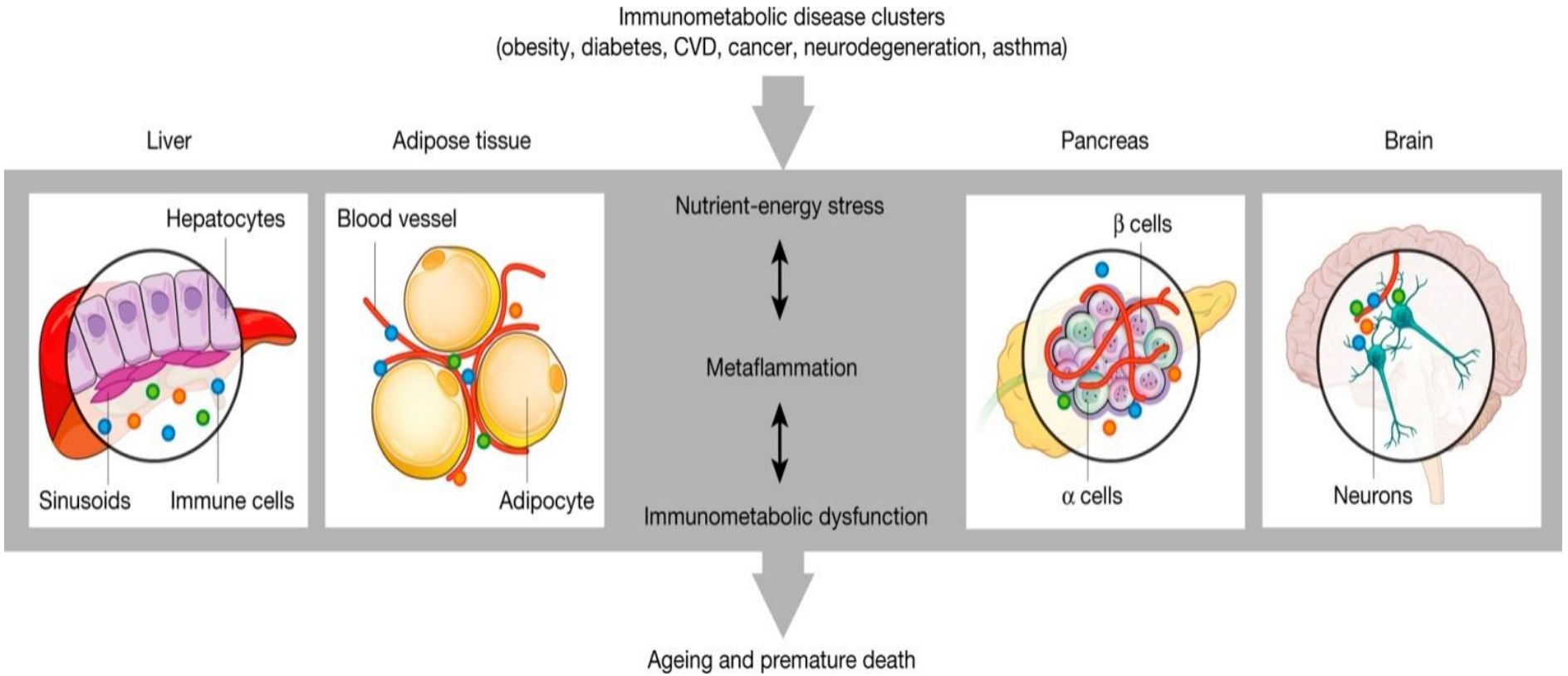
Development of inflammation in type 2 diabetes



Source: Type 2 diabetes as an inflammatory disease

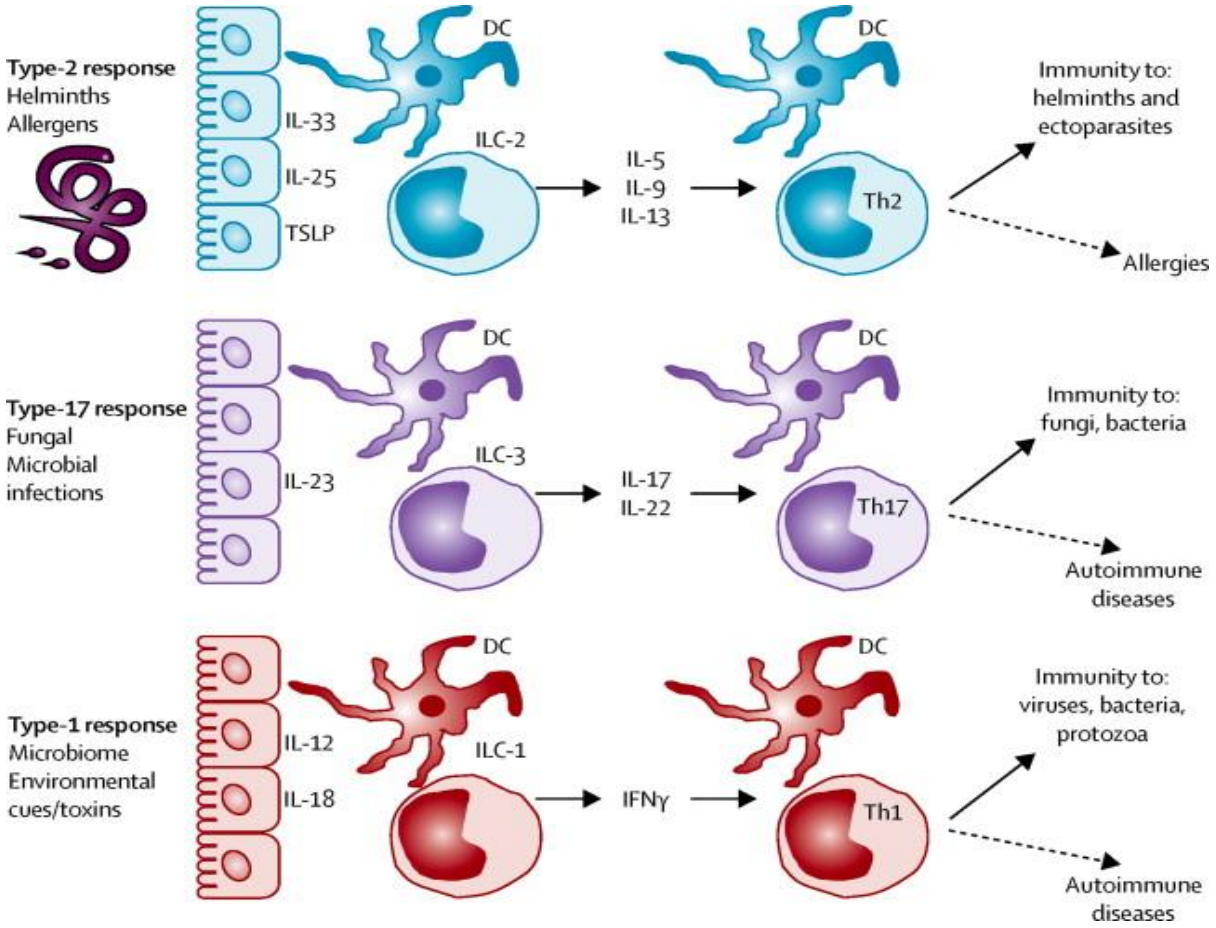
Marc Y. Donath & Steven E. Shoelson. Nature Reviews Immunology 11, 98-107 (February 2011)
doi:10.1038/nri2925

Immuno-metabolic impact of obesity on end organs



G S Hotamisligil *et al. Nature* **542,** 177–185 (2017) doi:10.1038/nature21363

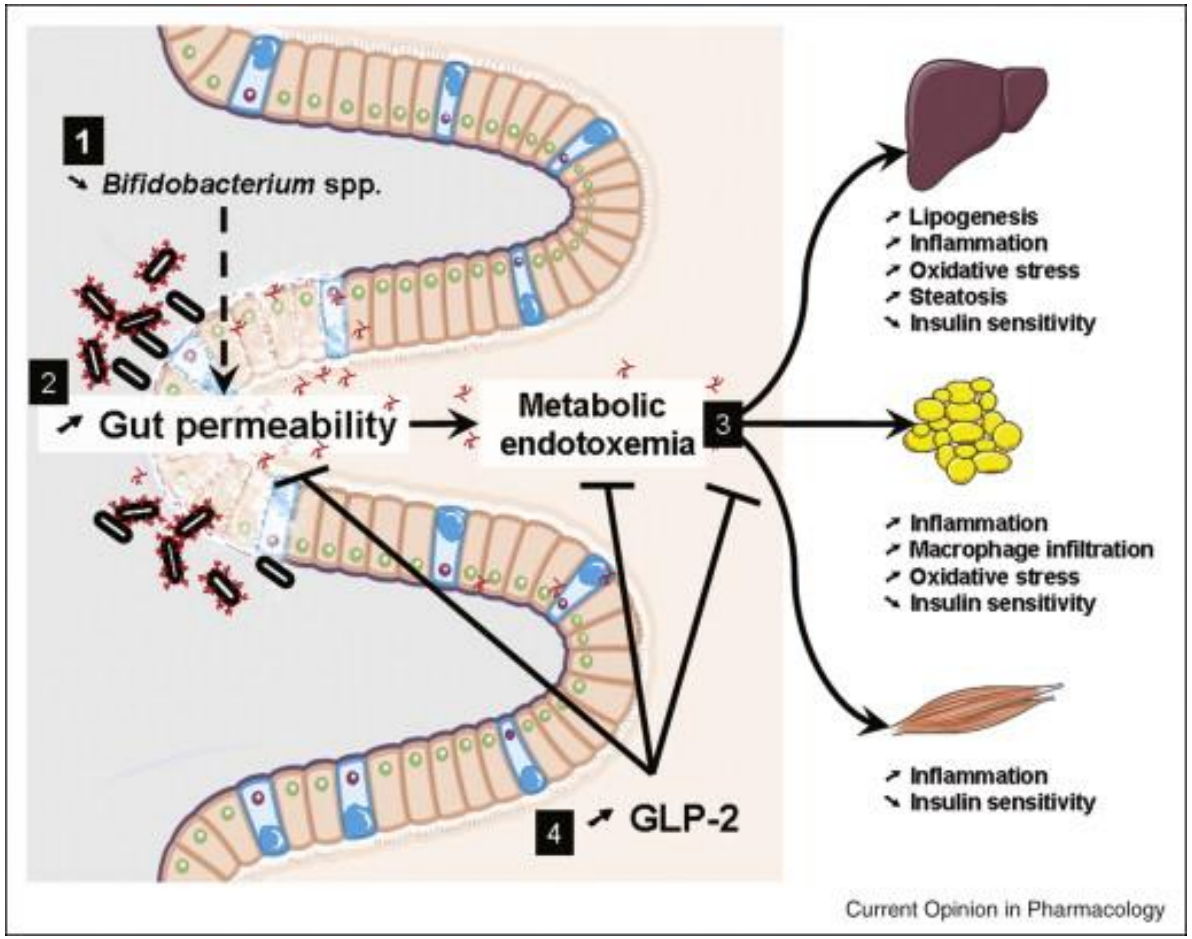
Polarisation of T-cell responses to incoming pathogens and environmental factors



At mucosal surfaces, epithelial and immune cells detect changes or danger in the environment. Dependent on the nature of the insult, cytokines are produced, which can drive the expansion of group 1, 2, or 3 innate lymphoid cells (ILC-1, ILC-2, and ILC-3) that in turn are associated with the induction of T-helper cells (ILC-1 is associated with Th1, ILC-2 with Th2, and ILC-3 with Th17). The different T-helper cells combat invading microorganisms. However, when uncontrolled, similar T-cell responses can lead to pathological conditions (shown by broken arrows). DC=dendritic cell. IL=interleukin. TSLP=thymic stromal lymphopoietin. IFN γ=interferon gamma.

Linda J Wammes, Harriet Mpairwe, Alison M Elliott, Maria Yazdanbakhsh Helminth therapy or elimination: epidemiological, immunological, and clinical considerations Lancet Infectious Diseases Volume 14, Issue 11, 2014, 1150–1162 http://dx.doi.org/10.1016/S1473-3099(14)70771-6

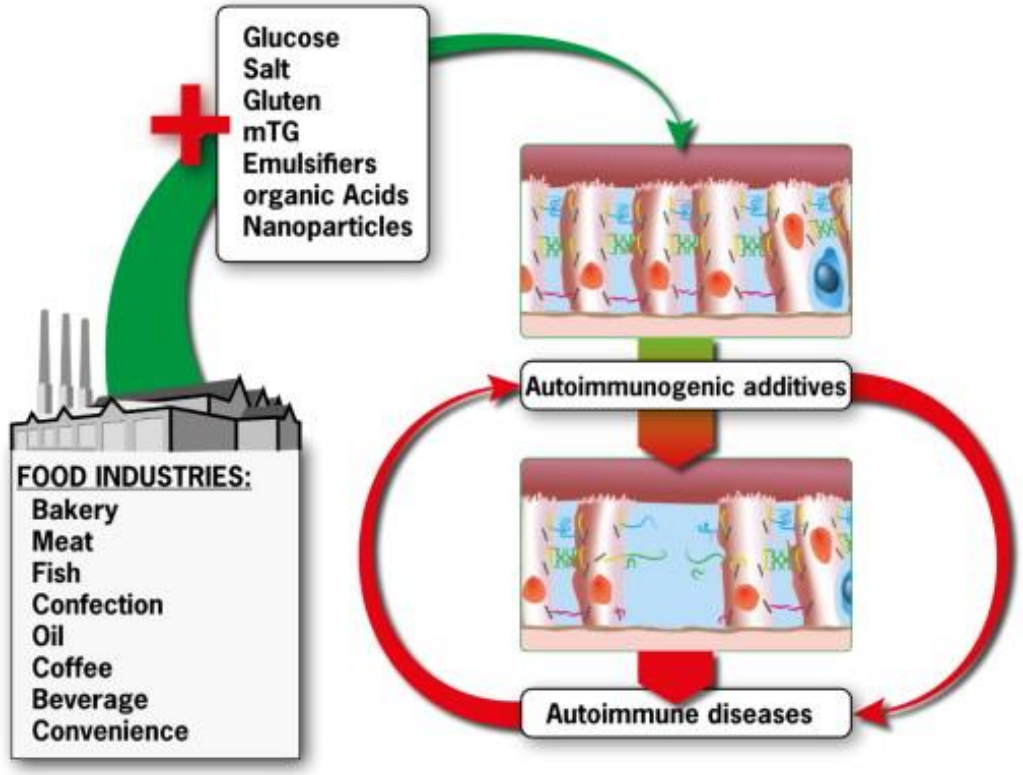
Changes in gut microbiota (following high-fat diet or obesity) promote gut permeability, increase metabolic endotoxemia and trigger the development of metabolic disorders.



Patrice D Cani , Nathalie M Delzenne ***Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota*** *Current Opinion in Pharmacology, Volume 9, Issue 6, 2009, 737 - 743*

http://dx.doi.org/10.1016/j.coph.2009.06.016

Do food additives disrupt tight junction permeability in the gut lining and can this lead to increased likelihood of autoimmune disease and chronic inflammation?



Schematic representation of the sequential steps through which industrial food additives induce autoimmune diseases. Commonly used industrial food additives abrogate human epithelial barrier function, thus increasing intestinal permeability

Aaron Lerner , Torsten Matthias Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease Autoimmunity Reviews, 2015
http://dx.doi.org/10.1016/j.autrev.2015.01.009

Hypothesis

Torres Strait Islanders living in different islands will have different exposure to processed foods, local fresh seafood and locally grown fruits and vegetables, and these exposures will result in differing metabolic, immunologic, nutritional and gut microbiota profiles.

The cases of Waiben (Thursday Island – main service centre, n=125) and Mer (Murray Island – remote traditional home of Eddie Mabo – high intake of local fish and garden produce, n=101)

Mer and Waiben Islands

Mer December 2016

Some preliminary results

	Waiben, n=125	Mer, n=101
Mean age (y)	38.2 (14.9)	42.2 (18.6)
% diabetes	23	30
BMI	31.3 (7.3)	31.8 (7.2)
Waist circumference (cm)	103 (17.3)	112.3 (17.7)
HbA1c (%)	5.9 (1.3)	6.2 (1.7)
Median Serum Folate (ng/ml)	10.8 (IQR 8.1-13.2)	13.5 (IQR 10.1-17.6)
CRP (nmol/L)	0.4 (0.3-0.6)	1.4 (0.8-1.8)
LPS Binding Protein (µg/ml)	17.9 (15.4-23.1)	7.2 (6.1-8.0)
PHQ-9 score 15+ (%)	5.4 %	2.0%

Mer older, more diabetics, heavier, less depressed, higher serum folate but also higher CRP, lower LBP.
No difference in lipids, LFTs, TNFa, smoking rates.
Those reporting having takeaways the previous week were more likely to have raised LBP (>10) than those reporting no takeaways (RR 1.8, 95% CI 1.3-2.5)

Selected preliminary results FFA and oxylipins

	Waiben	Mer
LA µg/ml (SD)	72.3 (56.8)	38.5 (22.3)
13 HODE (LA, ng/ml)	0.4 (0.4)	1.4 (1.0)
Total n-6/n-3	6.6 (1.2)	5.5 (1.2)
9,10 EpHOME (LA ng/ml)	18.1 (17.2)	8.5 (5.4)
Omega-3 Index	5.7 (1.1)	6.8 (1.4)

Total Saturated and Mono fats similar
Those with low LBP (<10 µg/ml) more likely to have high 13-HODE (OR 6.69, 95% CI 3.79-11.8)
Those reporting no takeaways were more likely to have a high 13-HODE (>0.8): RR 1.4, 95% CI 1.08-1.8

What about old friends?

Hypothesis

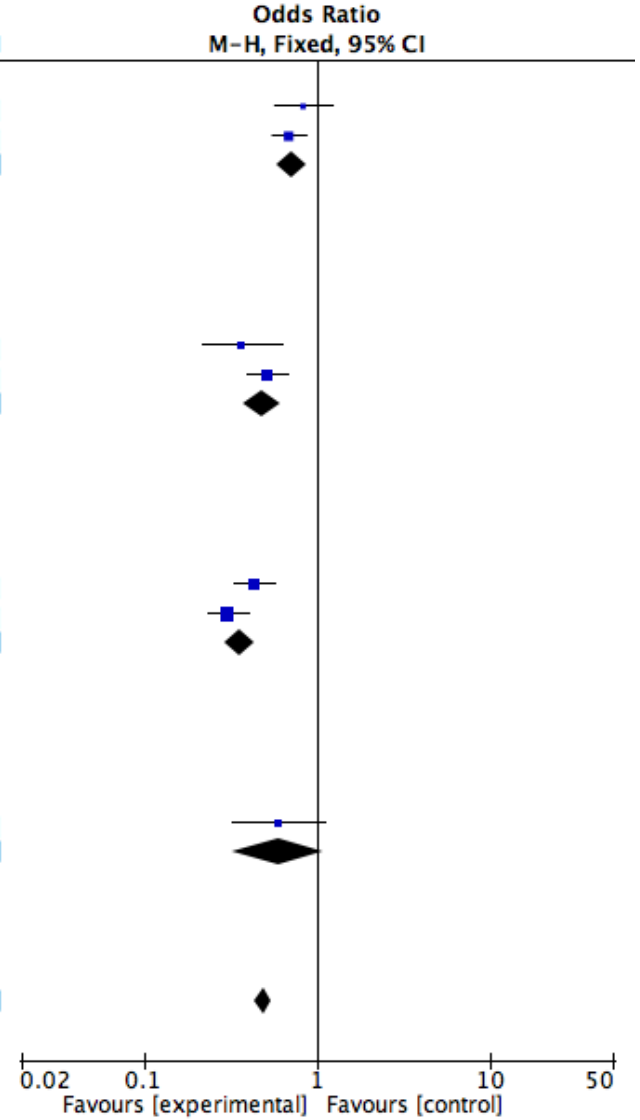
That intestinal helminth infection is protective against MetS and T2DM via a Th type 2 response and that this is mediated through the gut microbiota

- Several lines of evidence in human and animal models
- Preliminary data from JCU mice
- Preliminary data from human trials in celiac patients and in Indonesia
- Proposed phase 1 human trial of EHI commencing September 2017

Helminth infection protects against Metabolic Syndrome in humans: A meta-analysis of observational studies.

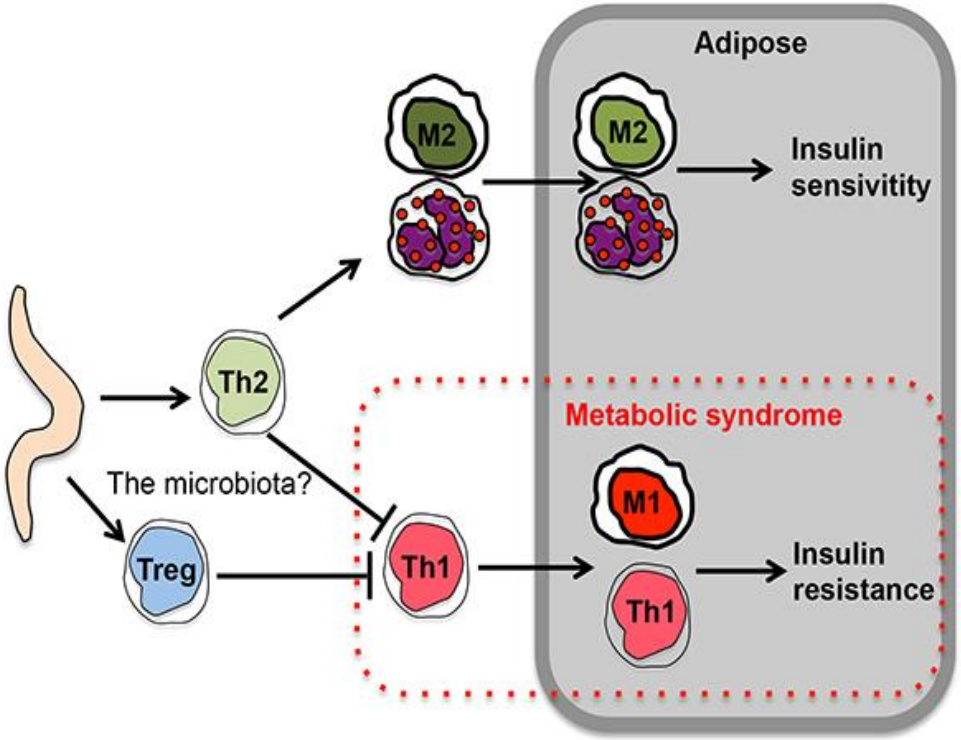
Combined OR=0.49 (0.44-0.55)

Study or Subgroup	Infection Events	Infection Total	No infection Events	No infection Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Hyperglycaemia (FBG > 5.6mmol/L)						
Wiria, hyperglycaemia	172	316	95	161	6.3%	0.83 [0.57, 1.22]
Shen hyperglycaemia	287	465	795	1133	19.4%	0.69 [0.55, 0.86]
Subtotal (95% CI)		**781**		**1294**	**25.7%**	**0.72 [0.59, 0.88]**
Total events	459		890			
Heterogeneity: $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0\%$						
Test for overall effect: Z = 3.29 (P = 0.001)						
1.4.2 Diabetes						
Hays, diabetes	32	92	99	167	5.0%	0.37 [0.22, 0.62]
Chen, diabetes	69	463	876	3450	19.4%	0.51 [0.39, 0.67]
Subtotal (95% CI)		**555**		**3617**	**24.4%**	**0.48 [0.38, 0.62]**
Total events	101		975			
Heterogeneity: $Chi^2 = 1.27$, df = 1 (P = 0.26); $I^2 = 21\%$						
Test for overall effect: Z = 5.93 (P < 0.00001)						
1.4.3 Metabolic syndrome						
Shen metabolic syndrome	85	465	385	1132	20.1%	0.43 [0.33, 0.57]
Chen, Metabolic syndrome	65	463	1207	3450	27.0%	0.30 [0.23, 0.40]
Subtotal (95% CI)		**928**		**4582**	**47.1%**	**0.36 [0.30, 0.43]**
Total events	150		1592			
Heterogeneity: $Chi^2 = 3.43$, df = 1 (P = 0.06); $I^2 = 71\%$						
Test for overall effect: Z = 10.61 (P < 0.00001)						
1.4.4 HOMA-IR > 90th %ile = 1.54						
Wiria, HOMAIR	26	316	21	161	2.8%	0.60 [0.32, 1.10]
Subtotal (95% CI)		**316**		**161**	**2.8%**	**0.60 [0.32, 1.10]**
Total events	26		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
Total (95% CI)		**2580**		**9654**	**100.0%**	**0.49 [0.44, 0.55]**
Total events	736		3478			
Heterogeneity: $Chi^2 = 30.18$, df = 6 (P < 0.0001); $I^2 = 80\%$						
Test for overall effect: Z = 12.27 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 25.64$, df = 3 (P < 0.0001), $I^2 = 88.3\%$						



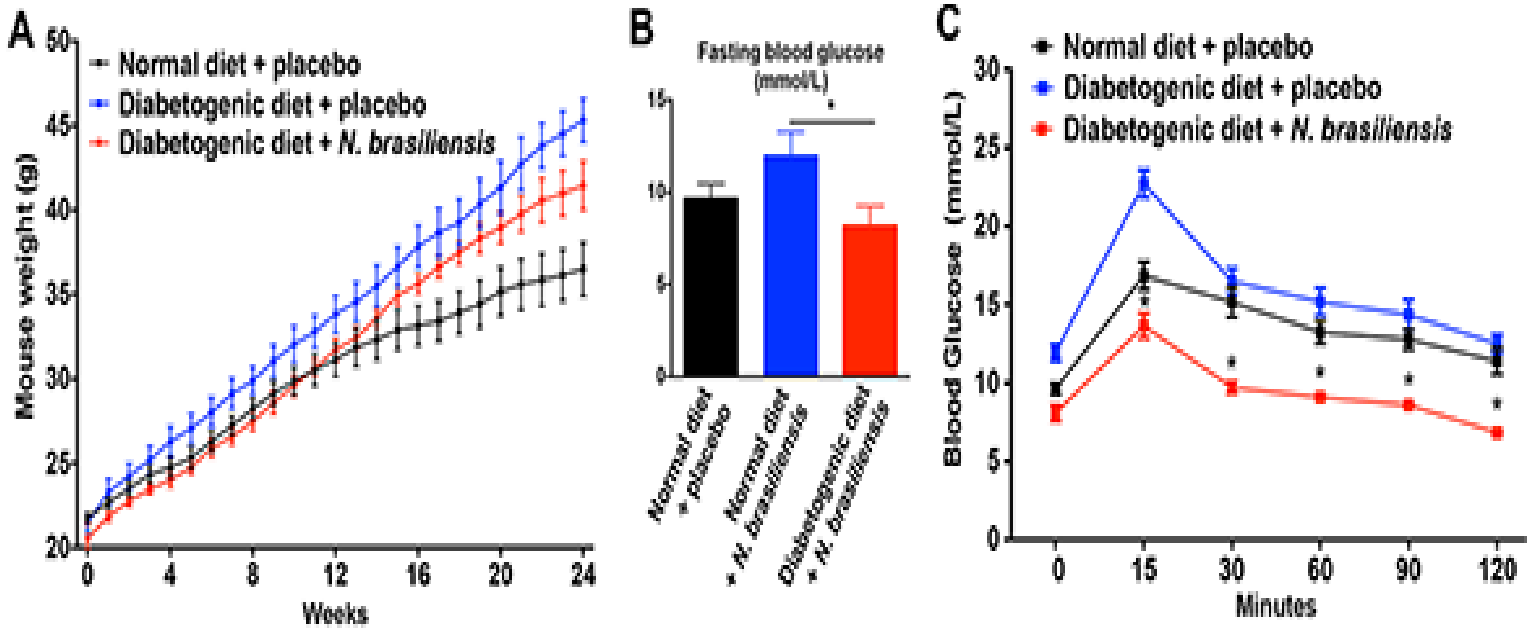
Source: Tracey, McDonald, McDermott. Diab Res & Clin Practice, 2015

Innate immunity and helminth infection – potential immunomodulatory impact of worms in the face of WAT-induced Th1 inflammatory cascade



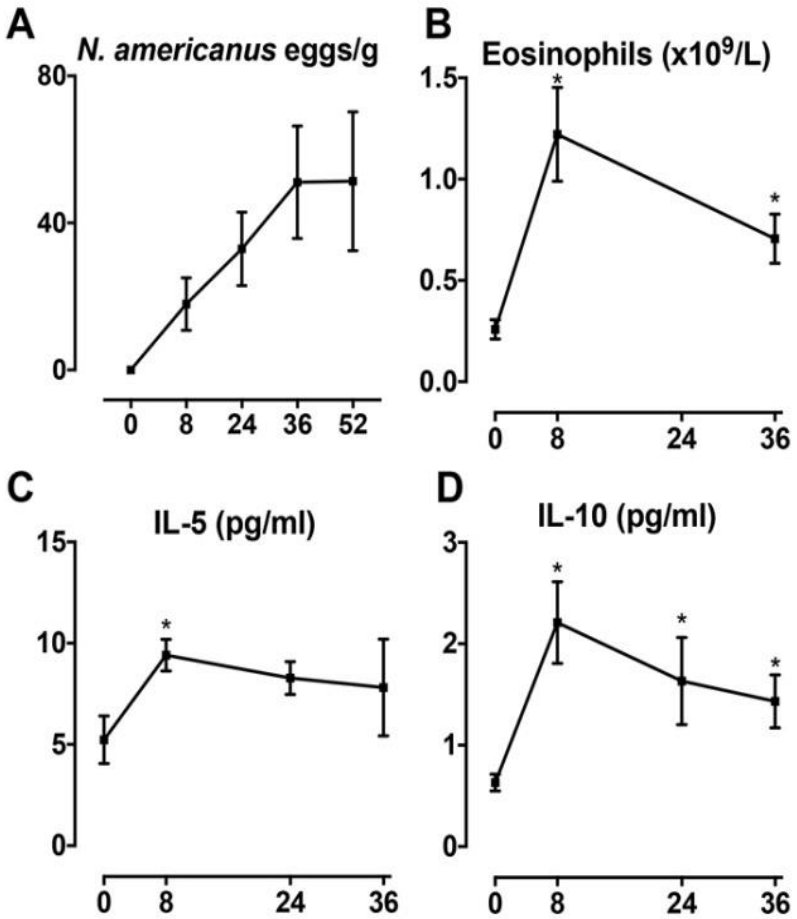
Helminth-induced protection against diabetes: potential mechanisms. T2DM and metabolic syndrome are associated with infiltration of the adipose with pro-inflammatory Th1 cells and M1 macrophages, which promote inflammation, insulin resistance, and hyperglycemia. Helminths may protect against this by supporting a Th2 or Treg response via mechanisms that may be dependent on the microbiota, promoting infiltration of the adipose tissue by M2 macrophages or eosinophils that improve insulin sensitivity.

Mouse model for T2DM, preliminary data, JCU 2016



Helminths closely related to human hookworm reduce metabolic disease parameters in mice. Mice were fed a normal or diabetogenic diet and treated with a placebo or *N. brasiliensis*. Mice treated with *N. brasiliensis* had **(A)** lower body weight (**B**) lower fasting blood glucose at 4 mo post-treatment and (**C**) Improved glucose tolerance after an oral glucose challenge at 6 months. *P<0.05 compared to diabetogenic diet + placebo.

Experimental hookworm infection alters systemic immune responses in humans

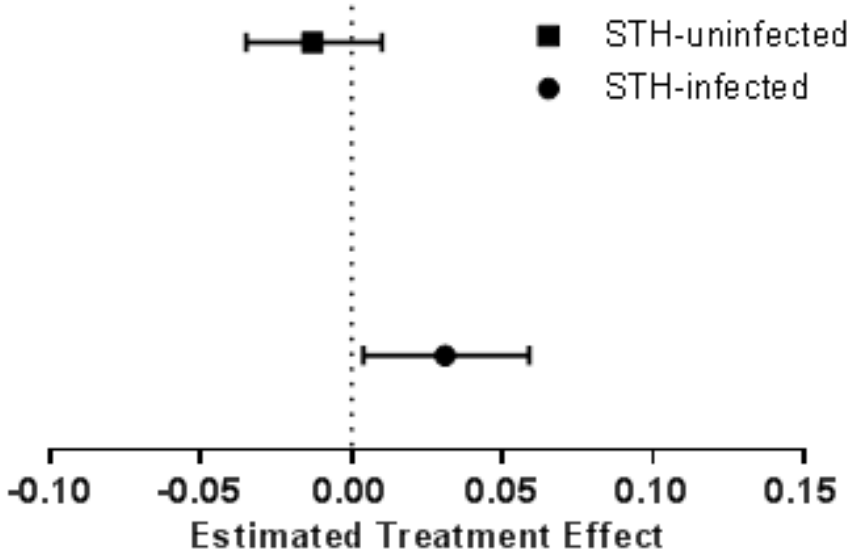


In our previous published coeliac trial we noted that (**A**) infections lasted at least a year in 100% of participants, characterised by parasite eggs in stool, (**B**) patients uniformly display blood eosinophilia (Croese et al., 2015). Unpublished data demonstrate that circulating (**C**) IL-5 and (**D**) IL-10 levels are also elevated by hookworm infection, suggesting that systemic Type 2 or regulatory immune responses can be influenced by an intestinal helminth infection. *P<0.05 compared to week 0.

Giacomin et al, 2017

Preliminary data from the SUGARSPIN trial (Flores),

Source: Supali,….Yazdanbakhsh et al unpublished data, March 2017



The primary outcome of the Sugarspin trial was that albendazole treatment in STH-infected subjects was associated with a significant increase in HOMA-IR [estimated treatment effect (95%CI): 0.032 (0.004-0.059), p=0.04].

Forrest plot graph (the dot represents the point estimate, while the line represents the 95%CI), for STH-infected subjects

Proposed Phase 1b RCT experimental hookworm infection in humans with MetS, 2017-19

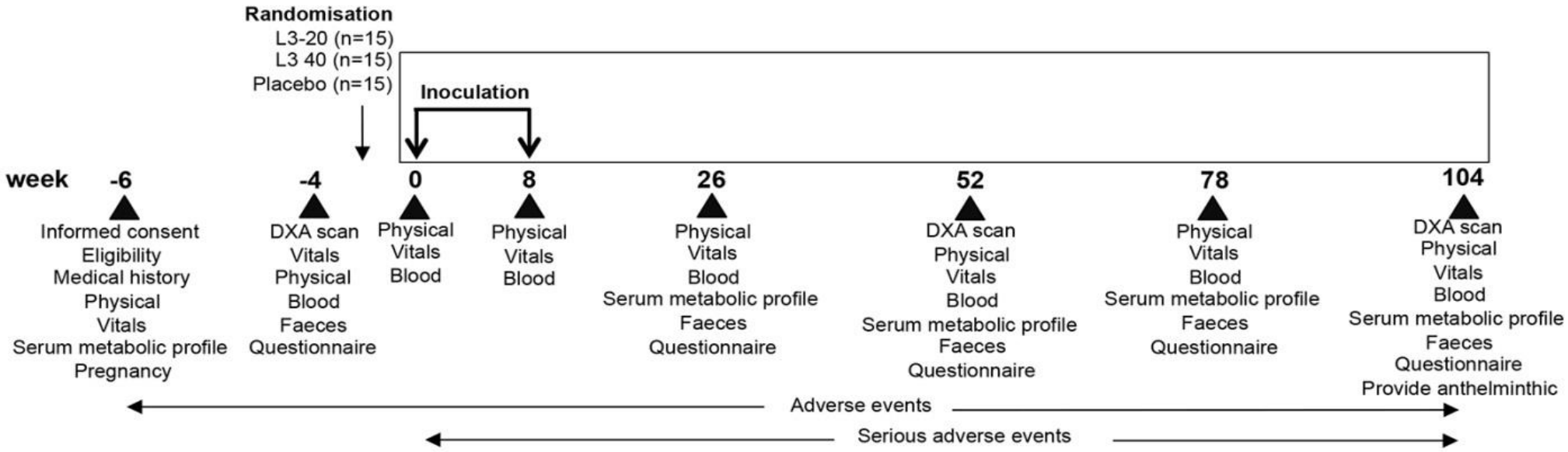


Fig. 4. Trial design and timeline.
Following screening, baseline analyses and randomisation, 45 participants will be allocated to receive placebo (histamine, n=15), low-level hookworm (2x10 L3 each, n=15) or medium-level hookworm infections (2x20 L3 each, n=15) at week 0 and week 8. Biochemical (serum profile) and physical indicators of safety and metabolic health will be assessed every 6 months during the 2-year study. Immunological parameters will be assessed at time points indicated by a blood draw. Faecal samples will be taken at designated time points for analyses of parasite egg burden and the microbiome.

Other projects from CCDP Cairns

- Generational anemia in FNQ remote communities (Dympna Leonard)
- Depression and diabetes n the Torres Strait (Sean Taylor)
- Utility of fitbit devices in increasing physical activity among young Indigenous people in Cairns and Mossman (Ashleigh Sushames)
- Role of “psychological insulin resistance” in declining uptake of insulin among adults with oorly controlled diabetes in the Torres Strait (Sean Taylor)
- Allostatic load in young people of Yarrabah, correlation with self-reported depression (Max Berger)
- Increasing physical activity among young women in Cairns and TI (Karla Canuto)
- *Strongyloides stercoralis* and T2DM in a Kimberley community (Russell Hays)
- Potentally preventable hospitalisations in FNQ – role of chronic care systems and workforce mix (Odette Gibson, Linton Harriss, Mary O’Loughlin)
- A better Indigenous CVD Risk estimate based on linked cohort data from FNQ (Lea Merone, Philip Clarke)
- Cognitive function and metabolic health in the Torres Strait (Fintan Thompson)

Big Esso to…

TI Team: Charlotte Tambo, Yoko Nagaki, Sam Mills, Edna Sambo, Sam Jones, Andrew Morsu and community participants on Mer and Waiben.

JCU Team: Paul Giacomin, Alex Loukas, Linton Harriss, Sean Taylor, Sandy Campbell, Malcolm McDonald, Sally McDonald, Fintan Thompson, Andy Way, Chris Lewis.

In South Australia

Bob Gibson, Maria Makrides, Liu Ge

Geraint Rogers, Lex Leong, Frederick Mobegi