



Appearances can be deceiving: the TOFI_Asia cohort

Dr Ivana Sequeira on behalf of the PANA MAH program

.....highlighted in the TOFI_Asia study

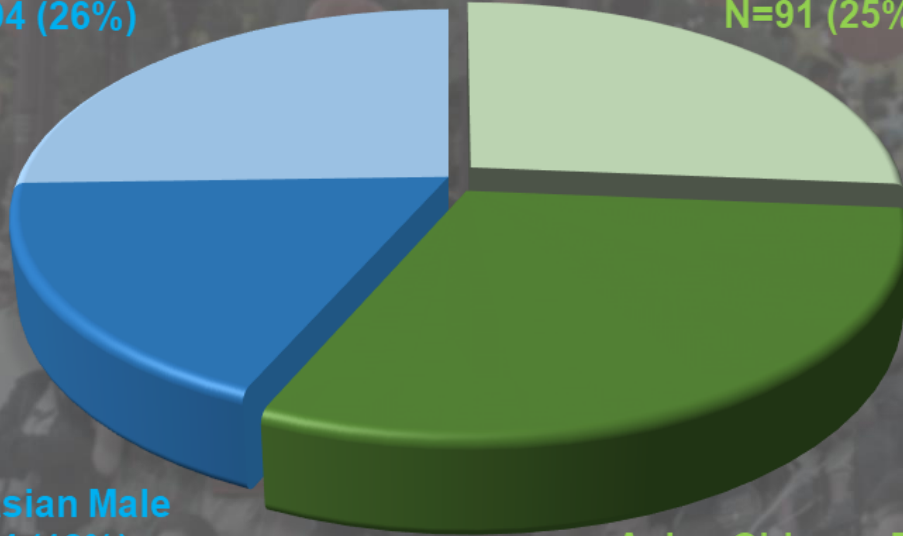


- Detailed phenotyping to determine new (early, more sensitive) markers of diabetes risk
- That are amenable to dietary (F&B) intervention

Recruitment of an important cohort

Caucasian Female
N=94 (26%)

Asian Chinese Male
N=91 (25%)



Caucasian Male
N=64 (18%)

Asian Chinese Female
N=108 (30%)

N=357 (158 Caucasian, 199 Asian Chinese)



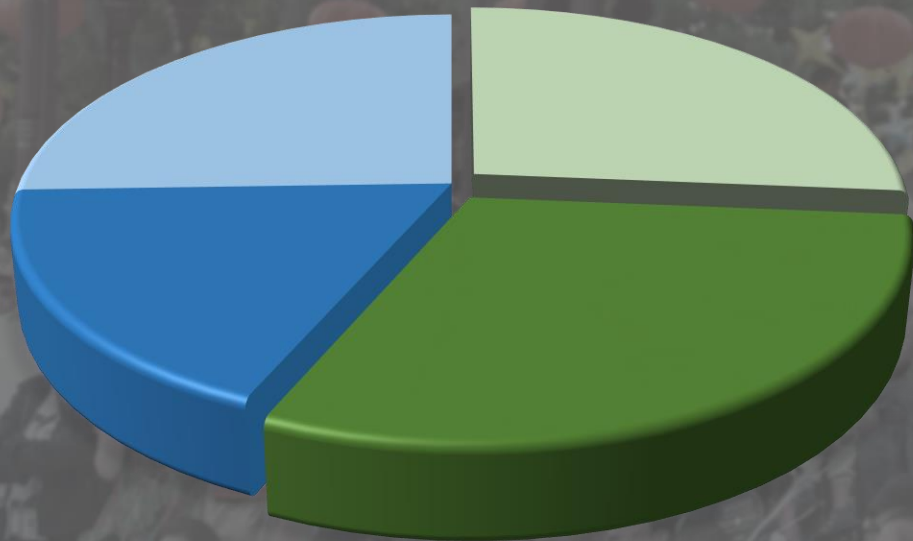
Dr Louise Lu



Wilson Yip (PhD)

Primarily migrated to New Zealand.....

40%*



99%*

Born outside
New Zealand

N=357 (158 Caucasian, 199 Asian Chinese)

* Data collected from a sub cohort of participants N = 177

✓ 158 European Caucasian

✓ 199 Asian Chinese

Both parents



18 – 70 yrs



20 - 45 kg/m²

healthy

Pre-Diabetic

TOFI_Asia study: Protocol

N = 357 ♀♂

199 Asian Chinese
158 Caucasian

Anthropometry



Height



Weight



Waist



Hip

TOFI_Asia study: Protocol

N = 357 ♀♂

199 Asian Chinese
158 Caucasian

Anthropometry

**Fasting blood
samples**

➤ ***Established markers***

Fasting plasma glucose

Hb_{A1c}

Insulin

GI Peptides

Amylin, Adiponectin

Full lipid profile

Liver function tests

Cytokines

TOFI_Asia study: Protocol

N = 357 ♀♂

199 Asian Chinese
158 Caucasian

Anthropometry

**Fasting blood
samples**

agresearch



Dr Karl Fraser



Emily Wu (PhD)

International collaborators



Dr John-Charles Martin



Prof Garth Cooper

- *Novel (metabolomics) markers*
Using an untargeted LC-MS

TOFI_Asia study: Protocol

N = 357 ♀♂

199 Asian Chinese
158 Caucasian

Anthropometry

**Fasting blood
samples**

DEXA scan



Auckland City Hospital



A/Prof Lindsay Plank

➤ *Total body and abdominal fat*

TOFI_Asia study: Protocol

N = 357



199 Asian Chinese
158 Caucasian

Anthropometry

Fasting blood
samples

DEXA scan

N = 68



34 Asian Chinese
34 Caucasian



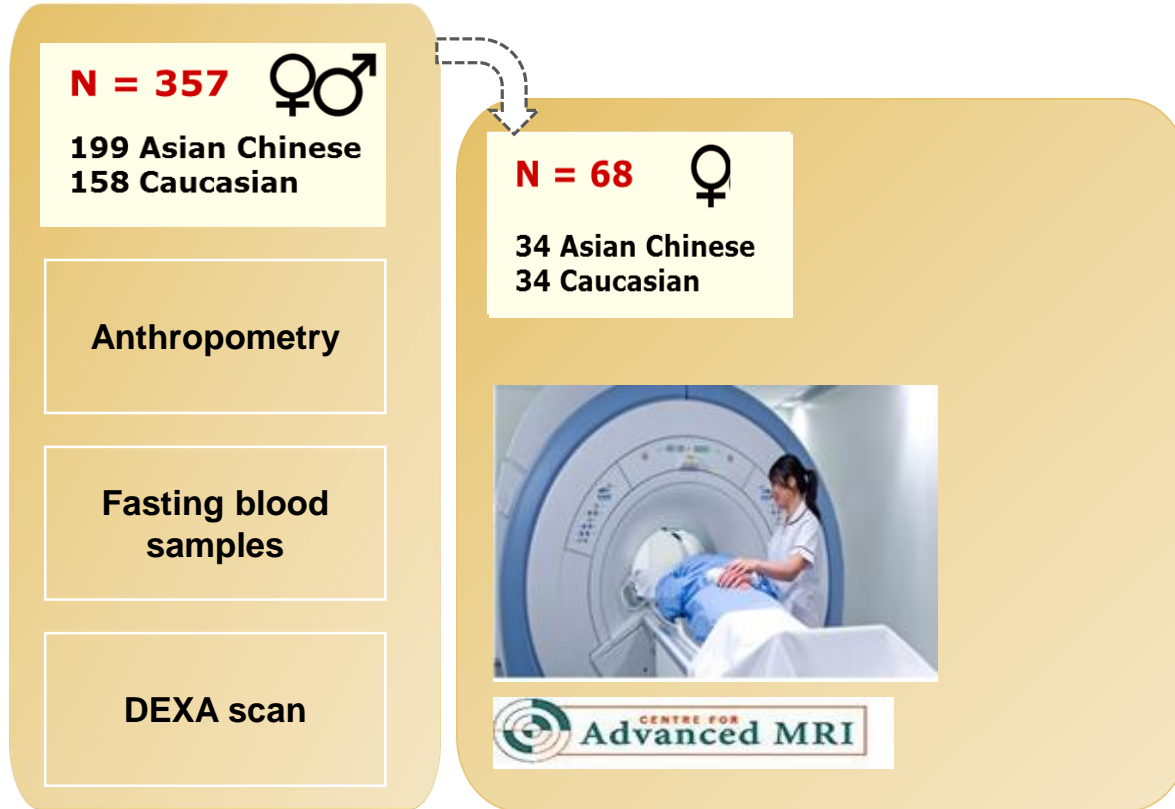
A/Prof Jun Lu



Dr Rinki Murphy

- *Lipid overspill into organs*
Pancreas fat, liver fat

TOFI_Asia study protocol



International collaborators
renowned for MR imaging



Dr. Keiren Hollingsworth

MR-OPSY METHOD*

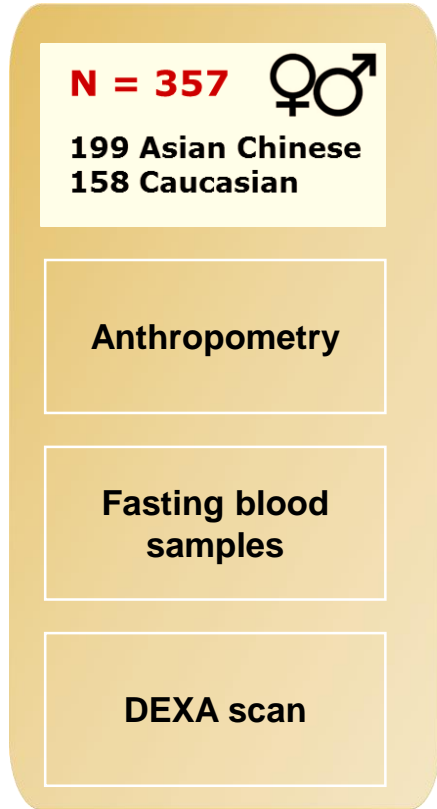
National
SCIENCE
Challenges

HIGH-VALUE
NUTRITION

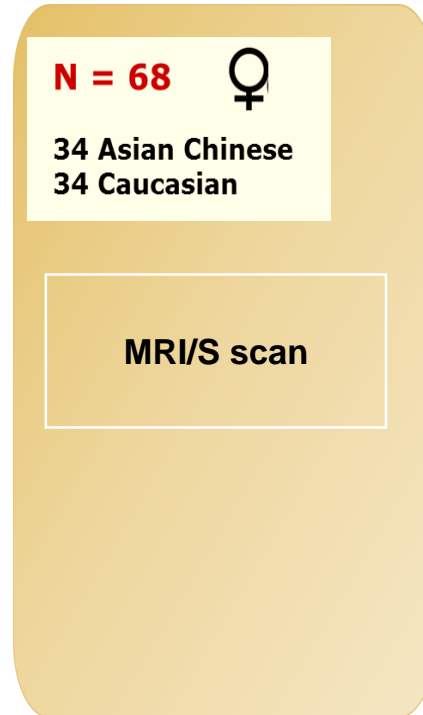
Ko Ngā Kai
Whai Painga

*Al-Mrabeh A *et al.* PLoS ONE 2017 12(4): e0174660; Crane JC *et al.* J Biomed Imag 2013:169256

TOFI_Asia Study: Findings



(i)



(ii)

TOFI_Asia Study: Findings

N = 357 ♀♂
199 Asian Chinese
158 Caucasian



	CAUCASIAN	CHINESE ASIAN	p value
Height (m)	1.72 ± 0.1	1.66 ± 0.1	<0.001
Weight (kg)	80.0 ± 15.7	75.6 ± 14.4	0.007
BMI (kg/m²)	26.9 ± 4.6	27.2 ± 3.9	ns
Age (yrs)	41.7 ± 16.1	40.5 ± 13.3	ns
Total body fat (%)	33.8 ± 10.2	35.0 ± 7.2	ns
Abdominal fat (%)	36.8 ± 14.1	40.8 ± 9.1	0.003

NOT AS TALL

Mean ± SD

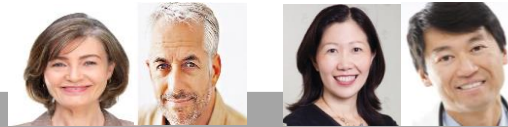
Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

Ko Ngā Kai
Whai Painga

TOFI_Asia Study: Findings

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WEIGHED LESS

Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

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Whai Painga

TOFI_Asia Study: Findings

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but **SIMILAR BMI**

Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

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TOFI_Asia Study: Findings

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SIMILAR AGE

Mean ± SD

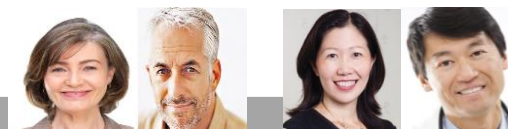
Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

Ko Ngā Kai
Whai Painga

At same Age and BMI – higher central adiposity

N = 357 
 199 Asian Chinese
 158 Caucasian



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DEXA

**GREATER
 ABDOMINAL FAT**

Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
 NUTRITION

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Weight (kg)	80.0 ± 15.7	75.6 ± 14.4	0.007
BMI (kg/m ²)	26.9 ± 4.6	27.2 ± 3.9	ns
Age (yrs)	41.7 ± 16.1	40.5 ± 13.3	ns
Visceral fat (%)	32.2 ± 19.9	39.7 ± 16.4	<0.001
Subcutaneous fat (%)	67.8 ± 19.9	60.3 ± 16.4	<0.001



**GREATER
 VISCERAL FAT**

DEXA
 Abdominal
 fat

Mean ± SD

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HIGH-VALUE
 NUTRITION

Ko Ngā Kai
 Whai Painga

TOFI_Asia Study: Findings

N = 357 ♀♂
199 Asian Chinese
158 Caucasian



Established
 BLOOD
 markers
 for
 diabetes
 risk

	CAUCASIAN	CHINESE ASIAN	p value
Fasting plasma glucose (mmol/L)	5.0 ± 0.6	5.3 ± 0.5	<0.001
Hb_{A1c} (mmol/mol)	33.3 ± 3.6	35.8 ± 3.9	<0.001
Triglycerides (mmol/L)	1.1 ± 0.6	1.4 ± 0.9	<0.001
HDL-C (mmol/L)	1.6 ± 0.4	1.4 ± 0.4	<0.001
ALT (U/L)	15.8 ± 10.3	19.3 ± 14.0	0.02
GGT (U/L)	23.6 ± 18.2	30.2 ± 23.8	<0.001

ALL HIGHER in Asian Chinese

Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
 NUTRITION

Ko Ngā Kai
 Whai Painga

TOFI_Asia Study: Findings

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ALT (U/L)	15.8 ± 10.3	19.3 ± 14.0	0.008
GGT (U/L)	23.6 ± 18.2	30.2 ± 23.8	0.003

LOWER in Asian Chinese

Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_Asia Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

Ko Ngā Kai
Whai Painga

At same Age and BMI – worse metabolic profile

N = 357 
 199 Asian Chinese
 158 Caucasian



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Fasting plasma glucose (mmol/L)	5.0 ± 0.6	5.3 ± 0.5	<0.001
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Liver
function
enzymes

BOTH HIGHER
in Asian Chinese

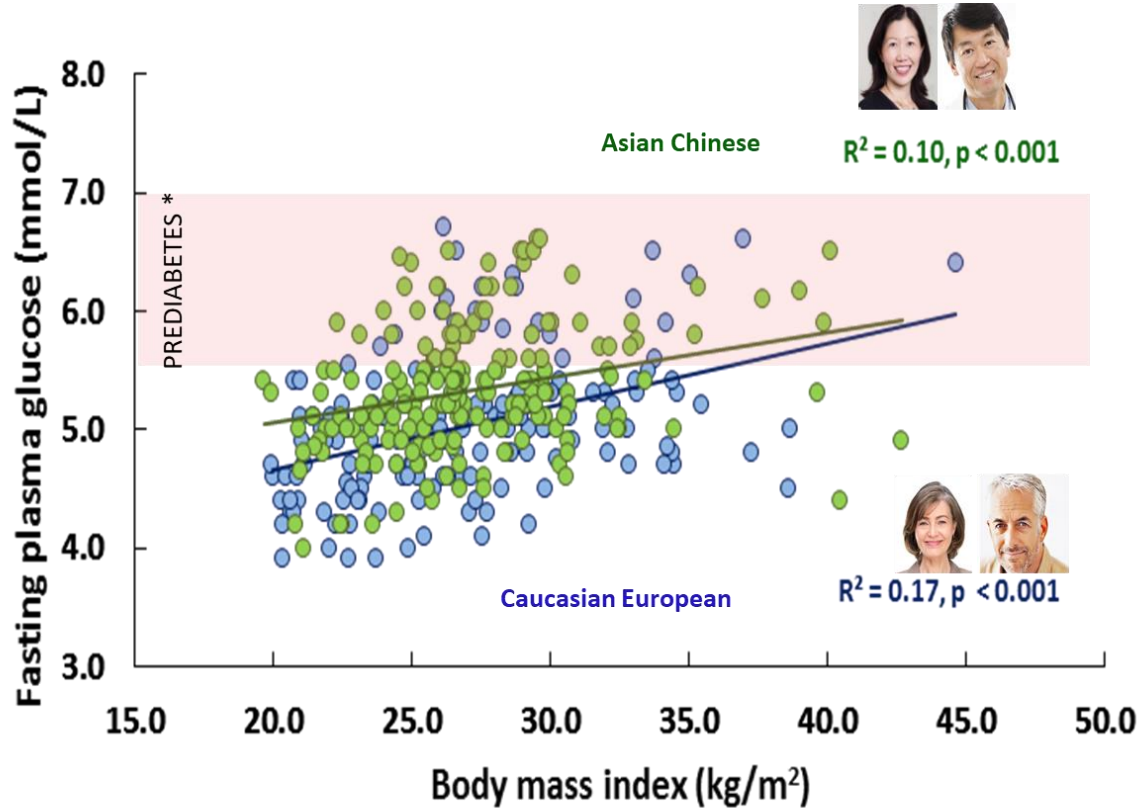
Mean ± SD

Sequeira IR et al. Predicting susceptibility to type 2 diabetes in an Asian Chinese and Caucasian cohort: the TOFI_{Asia} Study. For submission to Diab Obes Metab, 2019

HIGH-VALUE
NUTRITION

Ko Ngā Kai
Whai Painga

Established markers in the TOFI cohort

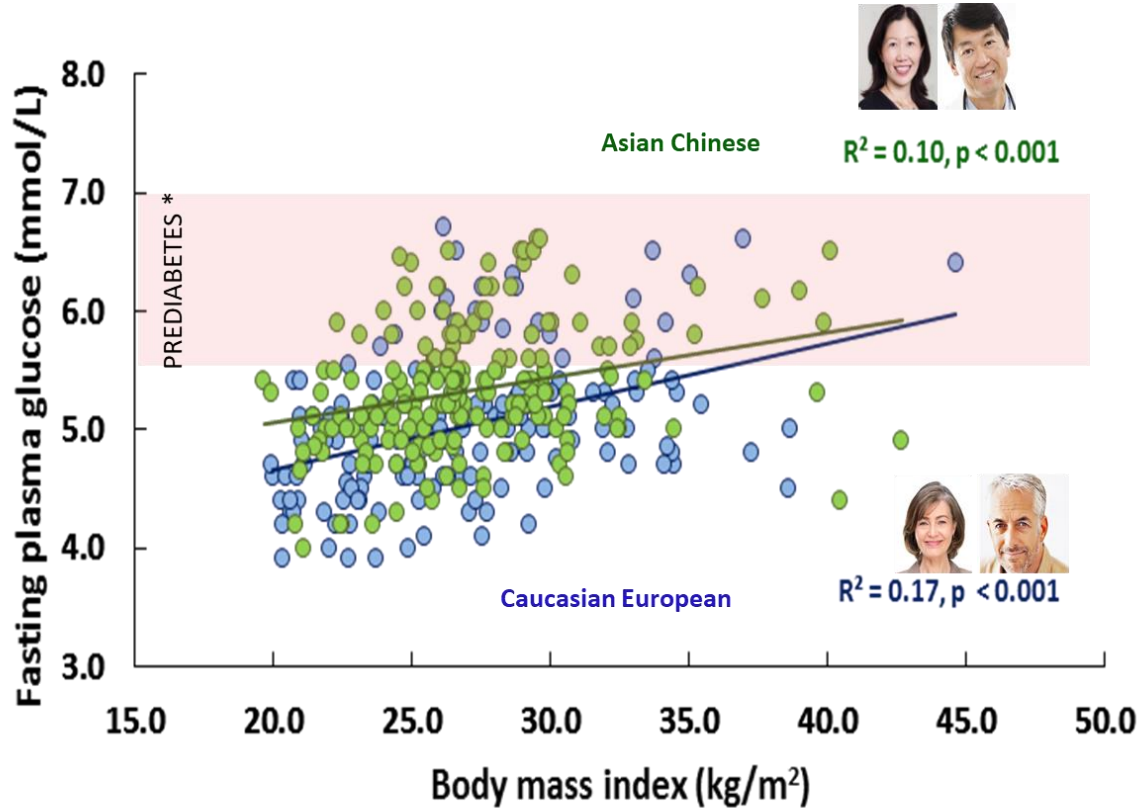


As expected, fasting glucose levels are significantly correlated with BMI in both Ethnicities

If anything higher in Asian Chinese at LOWER BMI

(Intercept: $t = 1.97, d.f. = 353, p < 0.05$)

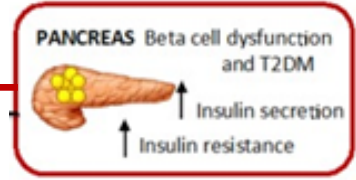
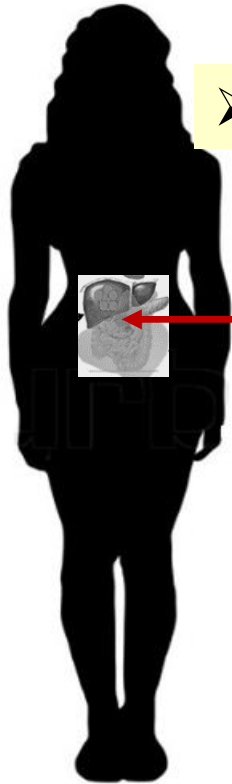
Established markers in the TOFI cohort



At LOWER BMI,
Asian Chinese had
HIGHER FPG
(0.3-0.5 mmol/L)
than Caucasians.

Is fasting glucose associated with increased pancreas fat?

➤ Pancreas fat may be an **EARLY** marker of T2D risk



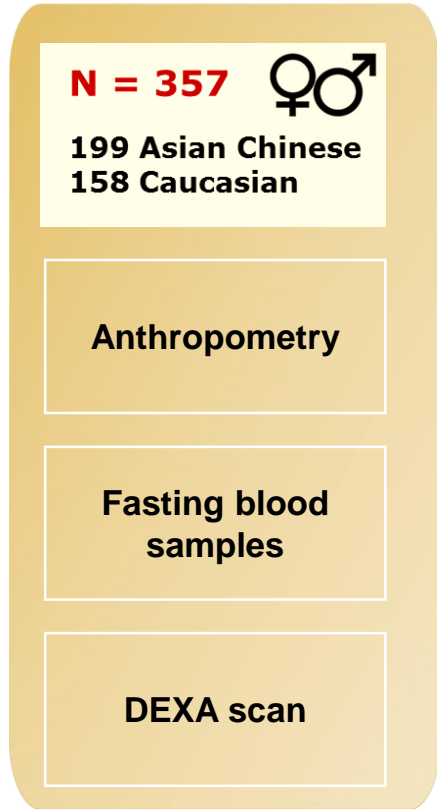
PANCREAS FAT (even in normoglycaemic individuals)



TOFI profile

INCREASED RISK

Is fasting glucose associated with increased pancreas fat?



(i)



(ii)



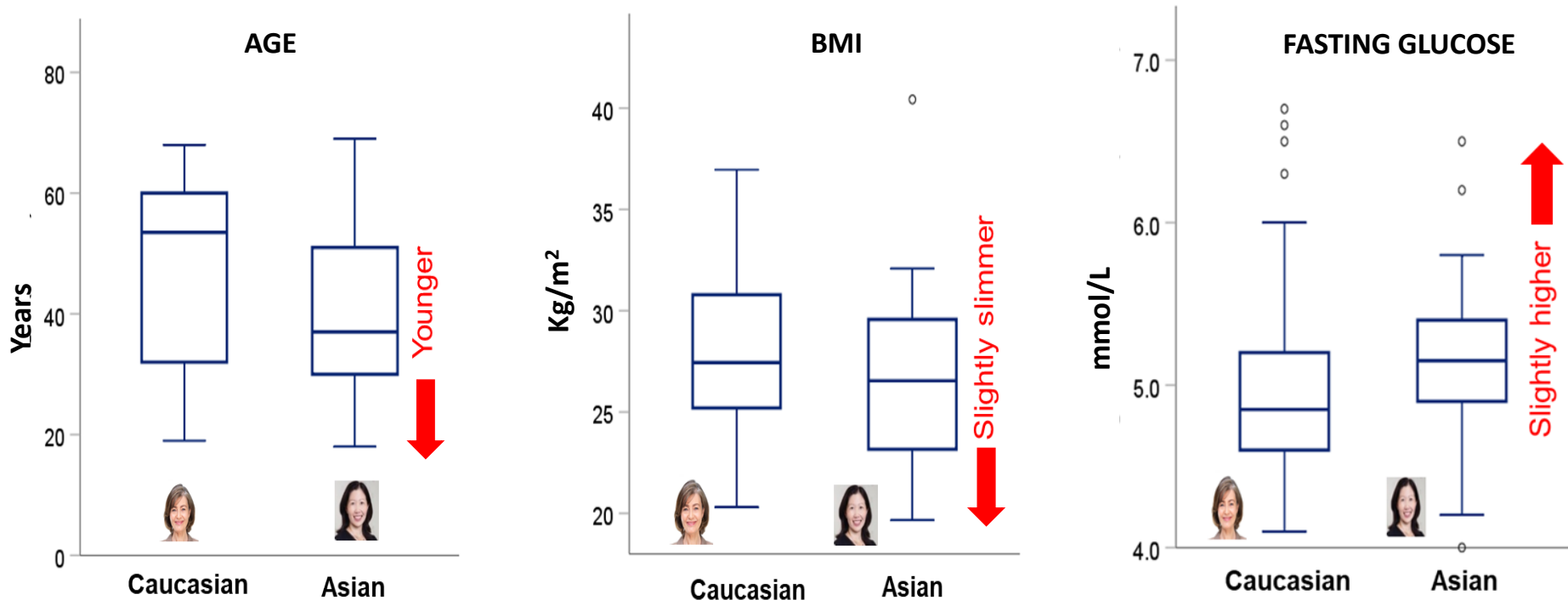
Only scanned **women**

- Due to gender differences in body composition

TOFI_Asia MR Study: Findings

N = 68 ♀

34 Asian Chinese
34 Caucasian



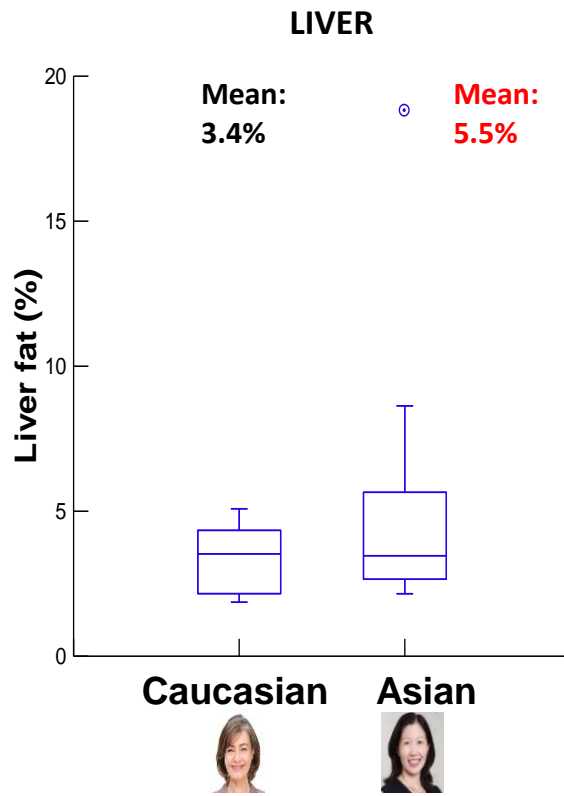
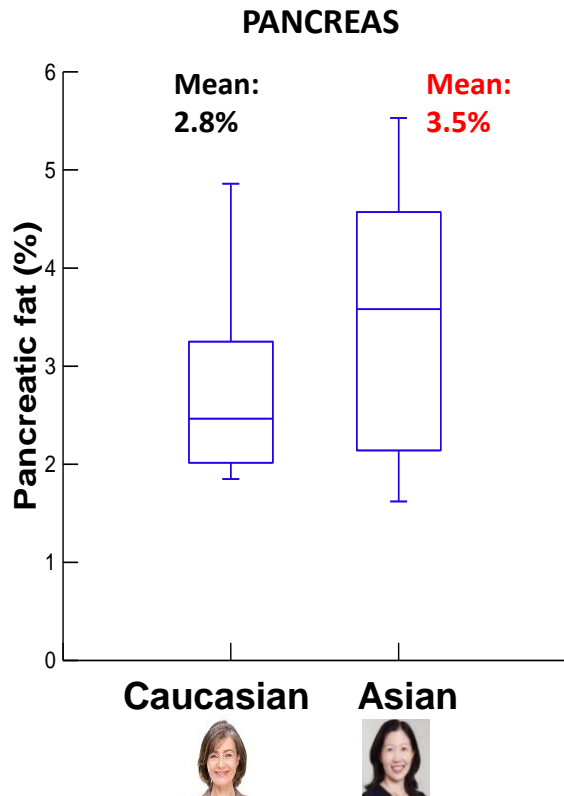
Box plots showing median and interquartile range

Sequeira IR et al. Does the 'thin on the outside fat on the inside' (TOFI) phenotype hide an increased metabolic risk due to ectopic lipid storage in the pancreas and liver: an MRI/MRS study. For submission to Diab Obes Metab, 2019

Organ fat in women with lower BMI.....

N = 68 ♀

34 Asian Chinese
34 Caucasian



**Higher in
Asian Chinese**

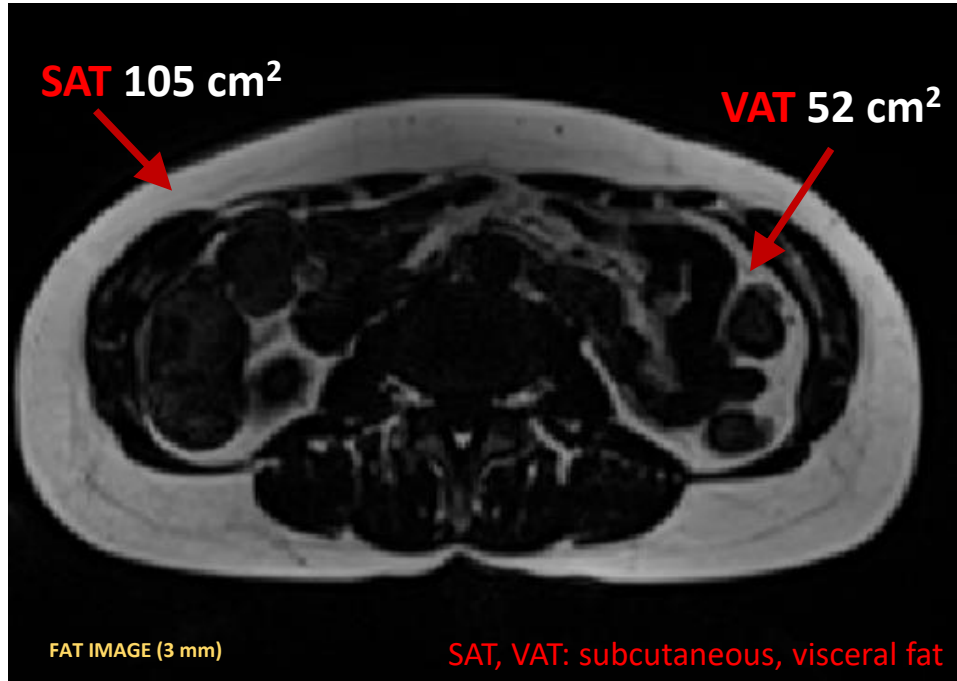
TOFI profile

Box plots showing median and interquartile range

MRI Scan

Caucasian female, 51 y

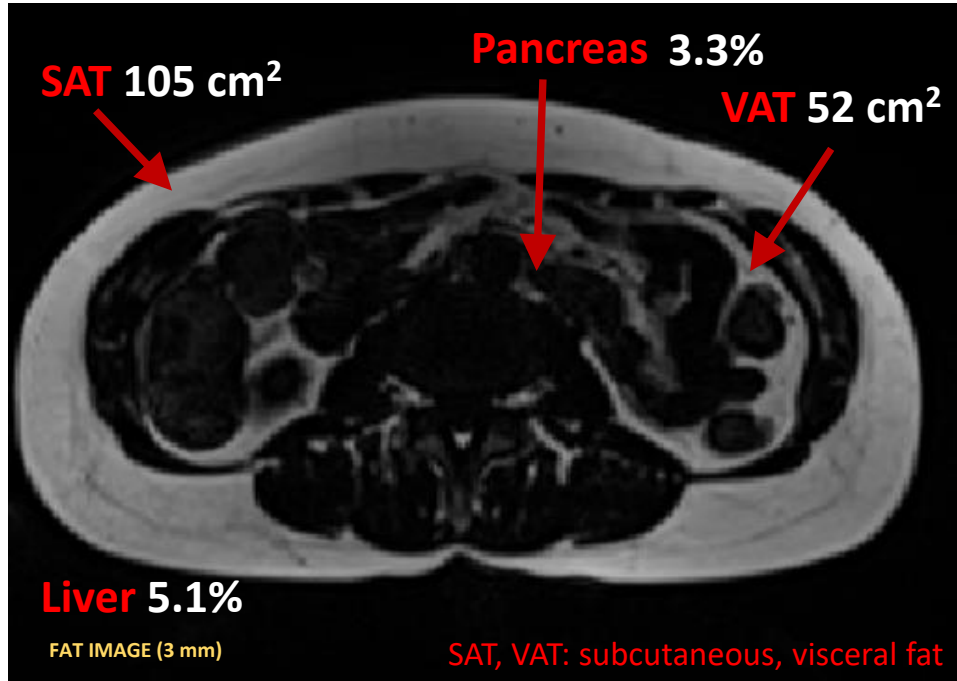
BMI 23 kg/m²



MRI Scan

Caucasian female, 51 y

BMI 23 kg/m²



Low Risk

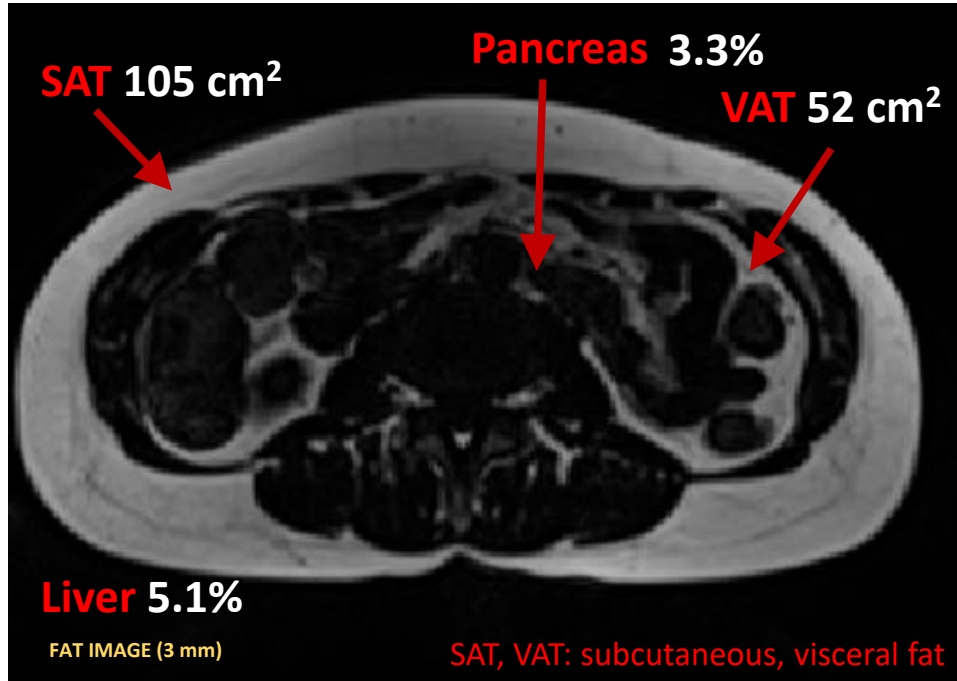


Fasting glucose
4.7 mmol/L

MRI Scan

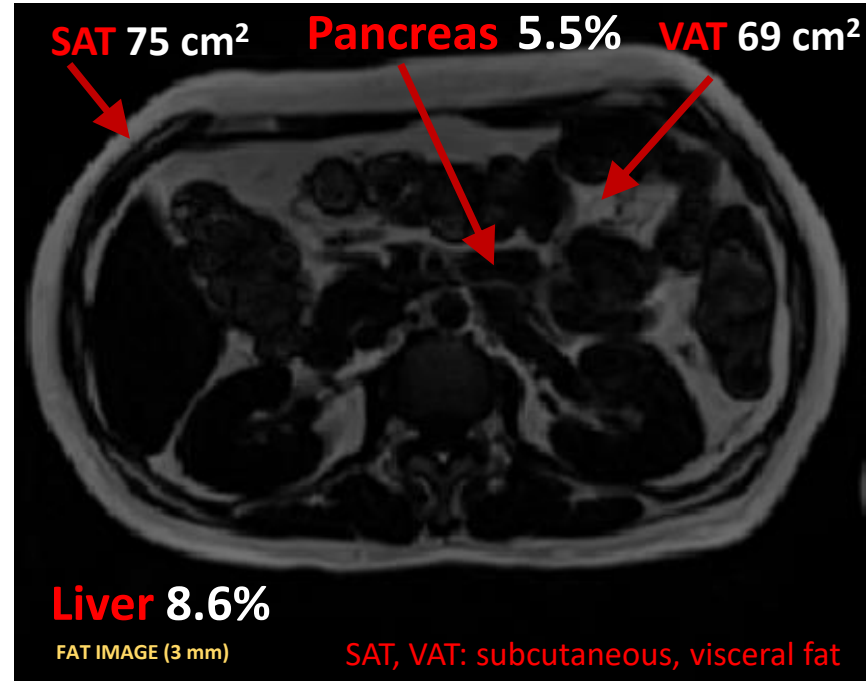
Caucasian female, 51 y

BMI 23 kg/m²



Asian Chinese female, 45 y

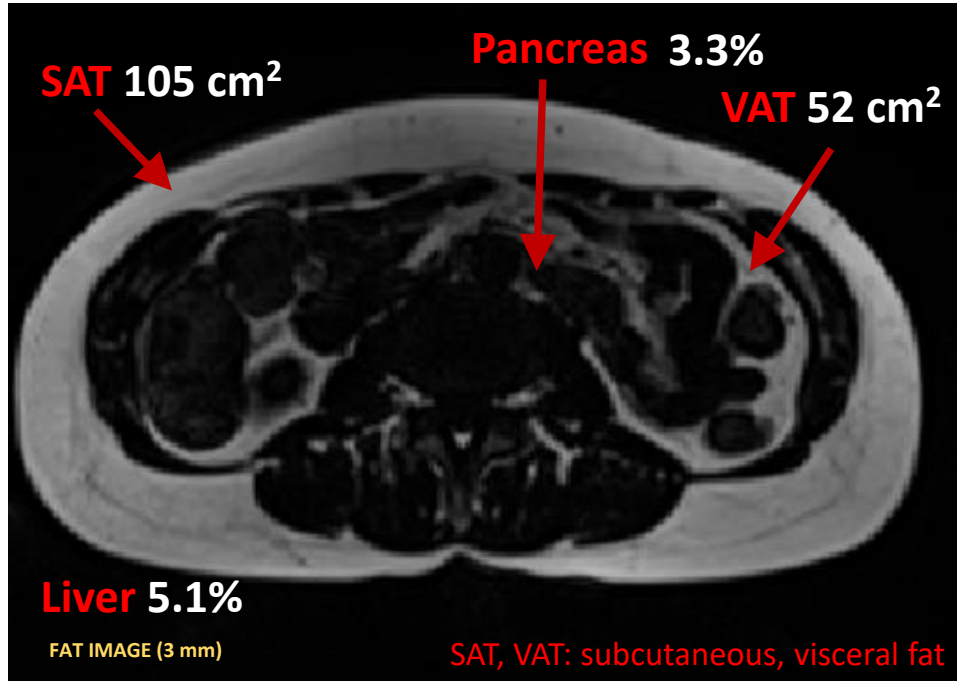
BMI 23 kg/m²



MRI Scan

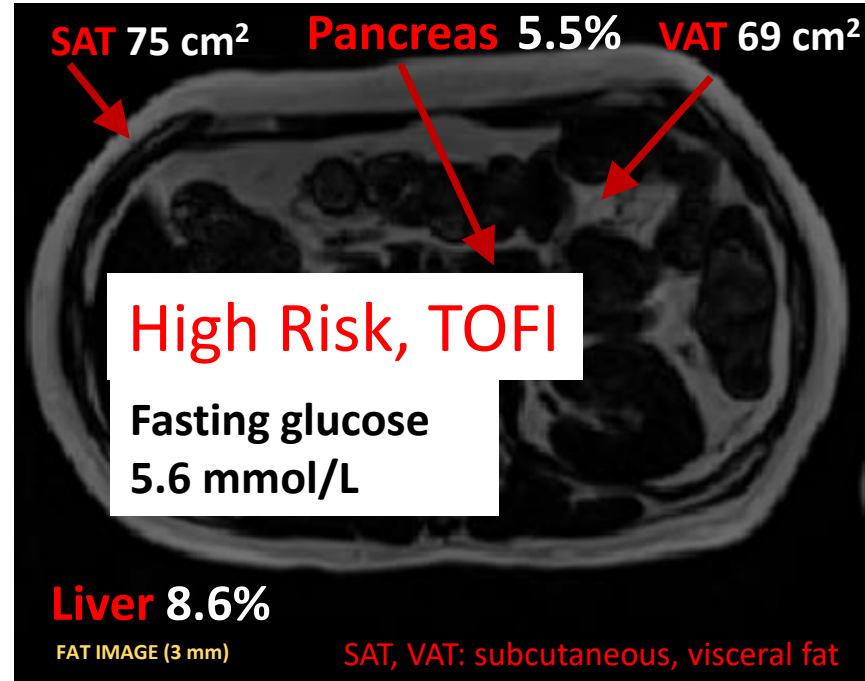
Caucasian female, 51 y

BMI 23 kg/m²



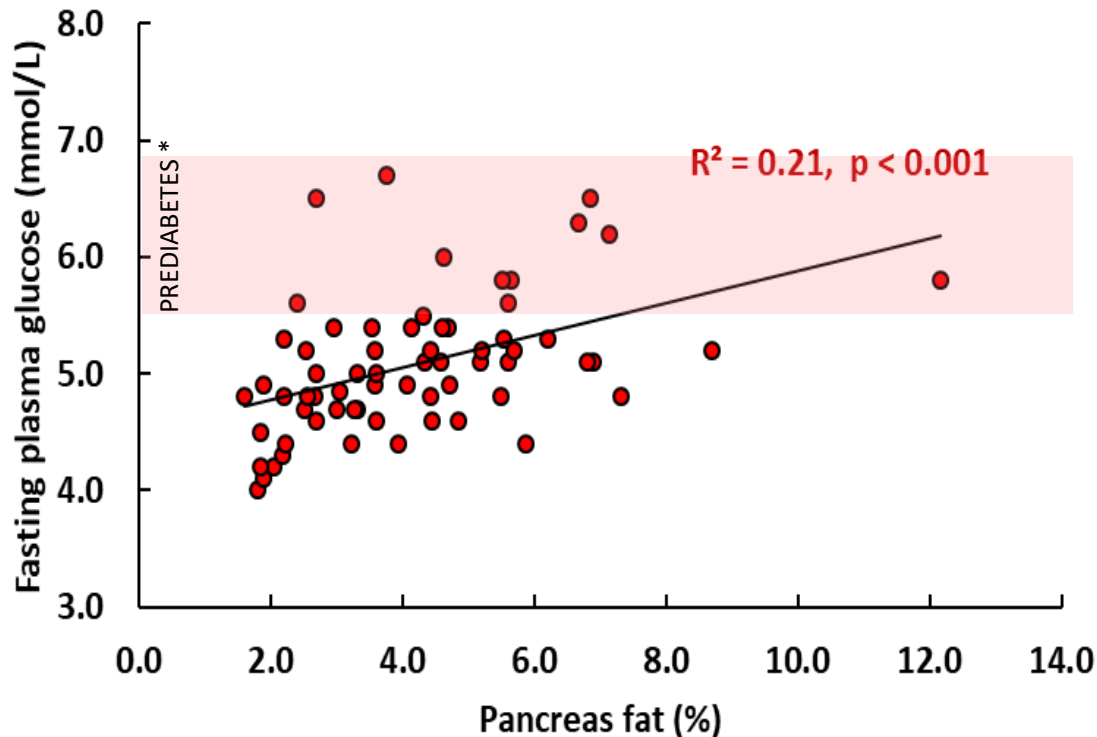
Asian Chinese female, 45 y

BMI 23 kg/m²



Relationships with fasting glucose

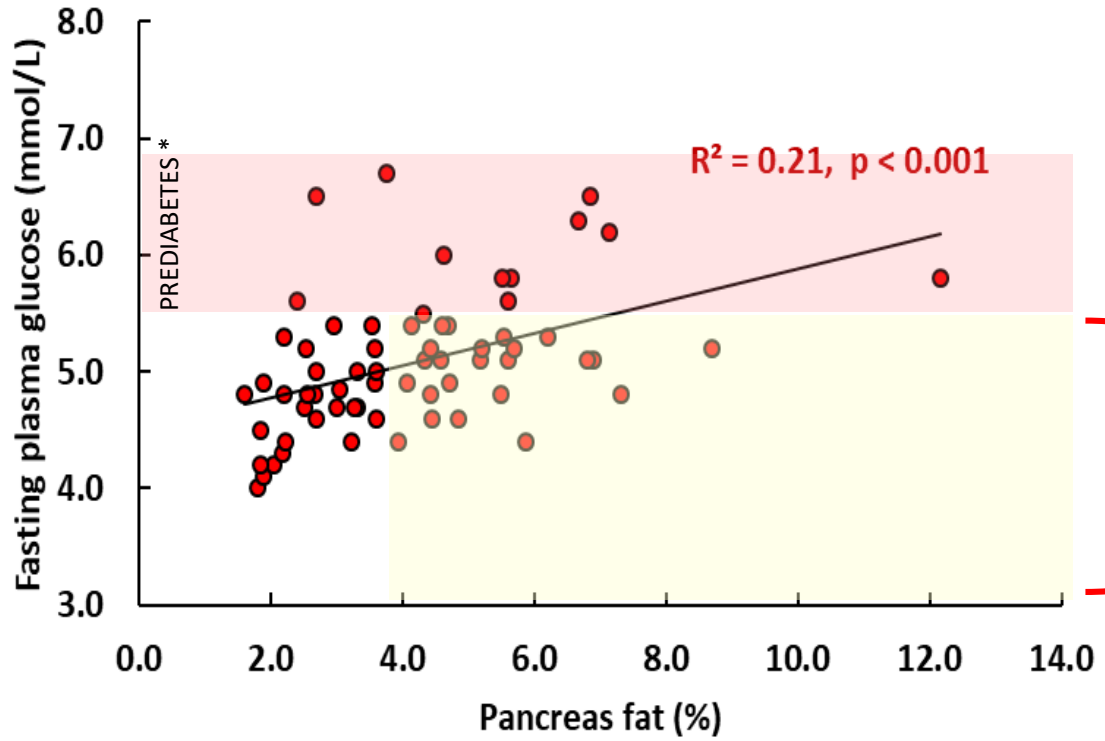
N = 68 ♀
34 Asian Chinese
34 Caucasian



➤ **PANCREAS FAT** maybe a possible **EARLY MARKER**

Relationships with fasting glucose

N = 68 ♀
34 Asian Chinese
34 Caucasian

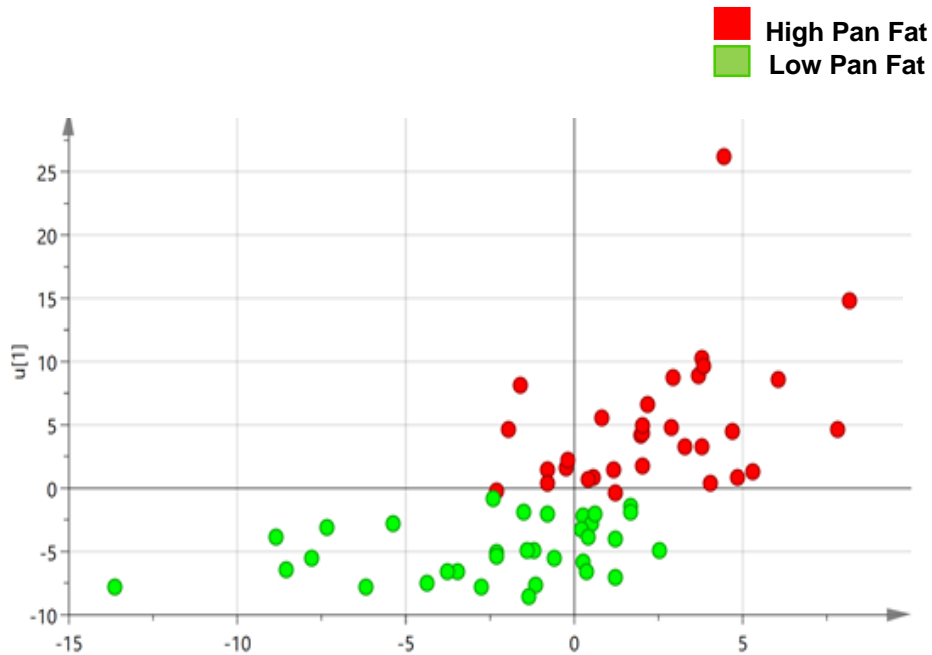


➤ *PANCREAS FAT maybe a possible EARLY MARKER*

May occur even before blood glucose levels rise and diabetes develops

* American Diabetes Association, 2016 Sequeira IR et al For submission to Diab Obes Metab, 2019

Identified novel (metabolomic) risk markers of pancreas fat



Dr Karl Fraser Emily Wu (PhD)

Blood metabolites correlated with high (red) and low (green) pancreas fat

NOVEL DATA - NOT YET PUBLISHED BY ANY OTHER INTERNATIONAL GROUP

Orthogonal partial least squares regression analyses, HILIC data
 $R^2Y = 0.64$, $Q^2 = 0.13$, $p = 0.08$

Wu Z et al. A metabolomic signature that reflects ectopic pancreatic fat in a cohort of healthy and pre-diabetic adults: data from the TOFI_Asia study. For submission to Diabetes, 2019

For more details about the Novel markers for pancreas fat

Metabolomics profiling of ectopic fat deposition in a cohort of Asian Chinese and Caucasian women in the TOFI_Asia study: an MRI substudy

Zhanxuan Wu^{1,2,6}, Karl Fraser^{3,5,6}, Marlana Kruger², Garth JS Cooper^{5,6}, Wilson Yip^{5,6}, Ivana R Sequeira^{5,6}, Sally D Poppi^{1,5,6}



¹ Food Nutrition & Health, Food and Bio-based Products, AgResearch Limited, Palmerston North, New Zealand; ² Institute of Food Science and Technology, Massey University, Palmerston North, New Zealand; ³ Rodent Institute, Palmerston North, New Zealand; ⁴ Centre for Food Safety and Experimental Therapeutics (CADET), University of Manchester, Manchester, UK; ⁵ Human Nutrition Unit, School of Biological Sciences, University of Auckland, Auckland, New Zealand; ⁶ High-Value Nutrition National Science Challenge, Auckland, New Zealand

Background

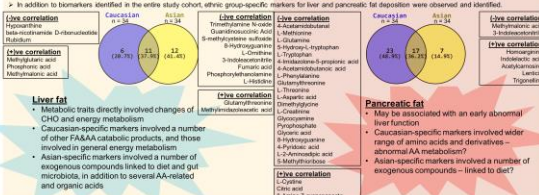
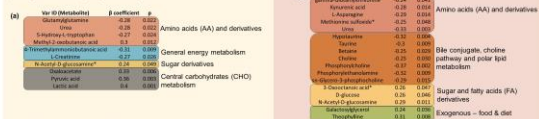
- Ectopic fat deposition has been proposed as a mechanism contributing to the early development and progression of pre-diabetes (1,2).
- Excess fat accumulating in essential endocrine organs such as pancreas and liver may take place well before symptomatic symptoms and diagnosis by clinical markers e.g. dyslipidaemia.
- Identifying systems biomarkers for and understanding the metabolic changes associated with ectopic fat deposition will aid early detection of abnormal metabolism well before the onset of the pre-diabetics and identify at-risk individuals.
- These biomarkers can also provide means to measure individual's response to nutrient intervention and act as indicators to show the effectiveness of an intervention in attenuating the condition.

Aims

- To characterise metabolic traits of magnetic resonance (MR)-assessed liver fat and pancreatic fat deposition in a cohort of Asian and matched Caucasian females using metabolomics approach
- To identify ethnicity-specific biomarkers for liver and pancreatic fat

Results

- Novel markers correlated with MRI-measured (a) liver fat, (b) pancreatic fat content identified by metabolomics (non-significant after adjusting for ethnicity).



Conclusion

- Metabolomics approach enables identification of novel biomarkers for pancreatic and liver fat and facilitates the understanding of the biology behind the metabolic traits
- Pancreatic fat is characterised by low levels of circulating AA and derivatives, bile conjugates and choline pathway metabolites, and high levels of glucose and fatty acids
- Liver fat is characterised by low levels of metabolism, amino acids derivatives and high levels of organic acids in the central CHO metabolism
- Sample stratification based on ethnicity further reveals different biomarkers for pancreatic and liver fat in Asian Chinese and Caucasian groups



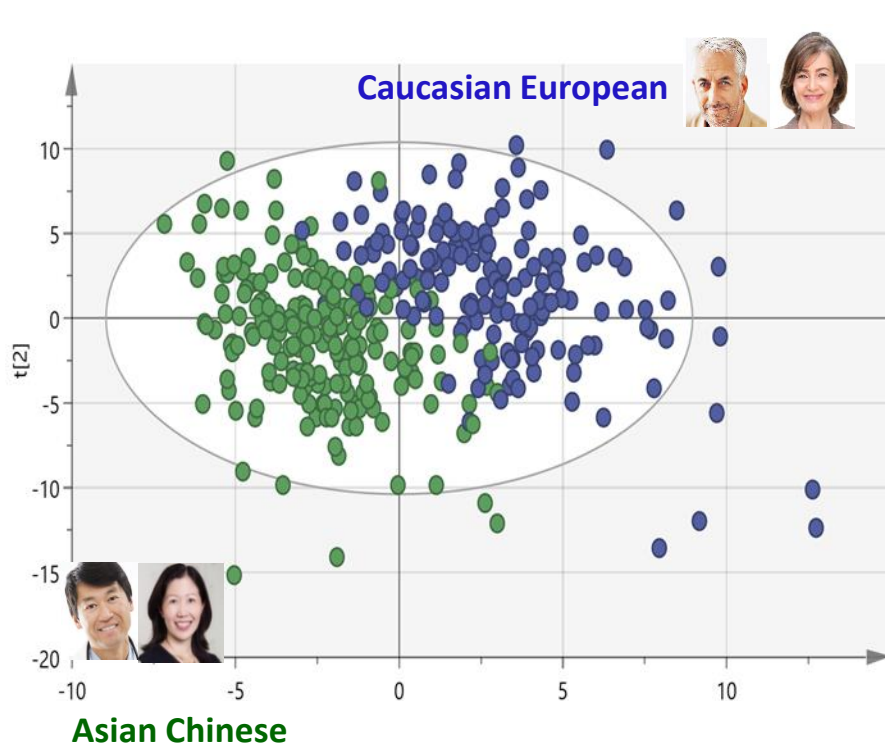
Emily Wu (PhD)

HVN Poster presentation I

Between the two ethnic groups

Wu Z *et al.* A metabolomic signature that reflects ectopic pancreatic fat in a cohort of healthy and pre-diabetic adults: data from the TOFI_Asia study. For submission to Diabetes, 2019

Identified novel markers in the full TOFI_Asia cohort (N=357)



Partial least squares discriminatory analyses, HILIC data
 $Q^2 = 0.678$, cross validation p value = 0

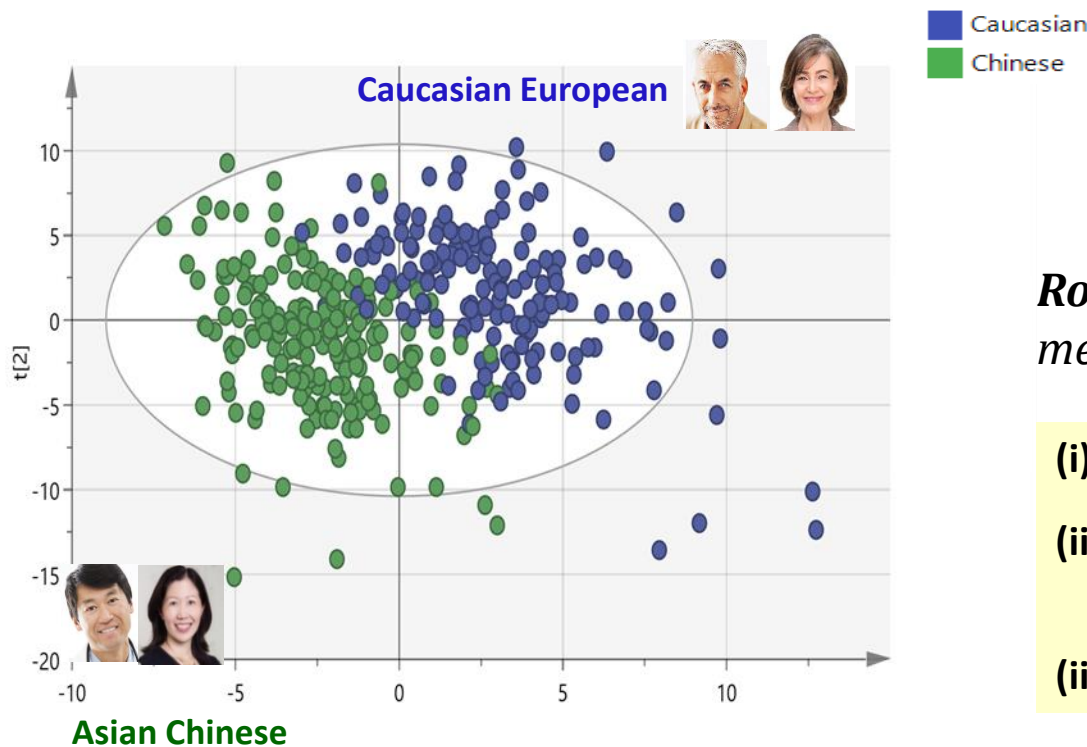
■ Caucasian
■ Chinese



Dr Karl Fraser Emily Wu (PhD)

Robust separation of blood metabolites: Caucasians (blue) and Asian Chinese (green)

Identified novel markers in the full TOFI_Asia cohort (N=357)



Robust separation of blood metabolites MAY BE DUE TO:

- (i) ETHNICITY
- (ii) PHYSIOLOGY/PATHOLOGY
(i.e. higher glucose)
- (iii) DIETARY DIFFERENCES

For more details on novel metabolomics markers (N=357)

Identification of novel biomarkers of pre-diabetes in a cohort of lean and overweight Asian Chinese and Caucasian adults: the TOFI Asia study^{1,2}

Zhanxuan Wu^{1,2,5}, Karl Fraser^{1,3,5}, Mariena Kruger^{1,3}, Garth JS Cooper^{4,5}, Wilson Yip^{1,6}, Ivana R Sequeira^{1,7}, Sally D Poppitt^{1,8,9}



¹ Food Nutrition & Health, Food and Bio-based Products, AgResearch Limited, Palmerston North, New Zealand; ² School of Health Sciences, Massey University, Palmerston North, New Zealand; ³ Medical Institute, Palmerston North, New Zealand; ⁴ Centre for Applied Dietary Medicine and Food, University of Reading, Reading, UK; ⁵ Centre for Applied Dietary Medicine and Food, University of Reading, Reading, UK; ⁶ School of Biological Sciences, University of Auckland, Auckland, New Zealand; ⁷ High-Value Nutrition National Science Challenge, Auckland, New Zealand

Background

Pre-diabetes is a dysglycaemic condition and predisposes individuals to development of type 2 diabetes (T2D) (1). The development of T2D in pre-diabetic individuals can be prevented by dietary intervention and lifestyle changes (2,3). Although metabolomics profile of T2D has been well documented, biomarkers of pre-diabetes are less studied and those reported ones to date have shown great diversity, which may depend on the study sub-population, gender, ethnicity, region and dietary pattern (4). This study aims to develop and apply a metabolomics-based approach for the identification of novel plasma biomarkers in a cohort of Asian Chinese and matched Caucasians. The identified markers will provide means to measure and report the effect of prevention dietary intervention to attenuate pre-diabetes and improve metabolic health.



Biomarker selection:

- Multivariate approach (PLS-DA) applied to pre-select important metabolites in decreasing FPG non-IFG based on variable importance (VIP > 1)
- Student t-test and simple logistic regression further applied to calculate p-value after multiple testing correction (p < 0.1)
- Multiple logistic regression further apply to adjust for ethnicity, gender, age and BMI on discriminatory metabolites (p < 0.05) to discover biomarkers associated with pre-diabetes independent of potential confounders

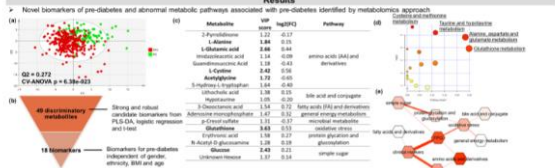
Pathway and network analysis:

- Metabolyze pathway analysis function using probed metabolite ID
- Cytoscape correlation-based analysis using partial correlation coefficient matrix

Predictive model for pre-diabetes:

- Multiple logistic regression containing different markers to yield best model performance (assessed by AUC, AUC permutation p-value and AUC after 10-fold cross-validation)

Results



(A) Robust PLS-DA model showed good separation between IFG vs IFG individuals

(B) 18 metabolites were identified as discriminatory metabolites that are important contributors driving the separation observed in PLS-DA plot (VIP > 1, least and logistic regression p-value after multiple testing correction < 0.1). 18 biomarkers remain significant after adjusting for potential confounders with multiple logistic regression for the separation of fasting glucose by a range of endogenous metabolites; top 10 VIP-ranked metabolites; top 10 VIP-ranked metabolites; top 10 VIP-ranked metabolites

(C) Pathway-based and (D) partial correlation-based network analysis of these metabolomics markers reveals abnormal metabolic pathways such as amino acid metabolism, protein modification, side metabolism associated with pre-diabetes state

(E) Predictive model for pre-diabetes combining traditional HbA1c and novel biomarkers identified by metabolomics approach

(F) HbA1c vs HbA1c + metabolomics markers

(G) Biomarker performance in the predictive logistic regression model

(H) Biomarker performance in the predictive logistic regression model

(I) Among the 18 biomarkers identified, combination of glutathione, L-cysteine and acetylglutamine, in addition to the traditional hyperglycaemic marker HbA1c, produced the strongest predictive model and is of better performance over using HbA1c alone

(J) Sensitivity of each variable in the predictive logistic regression model

(K) Glucose was excluded from the analysis since it can introduce multicollinearity and it doesn't add biological value to the model (impaired glucose level is the definition of IFG)

Conclusions

A metabolomics-based method has been developed to identify robust and strong biomarkers for pre-diabetes

Pathway analysis reveals altered metabolism of AA, FA, sugar and protein modification associated with pre-diabetes

Combination of novel and traditional markers (glutathione, L-cysteine, acetylglutamine and HbA1c) produced model with improved predictive performance than HbA1c alone

Next step: apply this approach to identify ethnicity-specific biomarkers, and explore potential link between pre-diabetes and other risk factors (e.g. insulin resistance) using the metabolomics data

References: (1) Cook DJ, et al. *Diabetes Care* 2005; 28(12): 2745-2751. (2) Knowler WC, et al. *Diabetes Care* 2002; 25(11): 1179-1191. (3) Knowler WC, et al. *Diabetes Care* 2002; 25(11): 1179-1191. (4) Poppitt SD, et al. *Diabetes Care* 2008; 31(12): 2145-2154

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Emily Wu (PhD)

HVN Poster presentation II

Based on fasting glucose levels

Building on our TOFI_Asia findings.....



European Caucasian



✓ Asian Chinese



PANaMAH Phase I: - - - - ->
TOFI_Asia study

Novel markers are sensitive to F&B intervention

Tū Ora Study
Collaboration with



12 week intervention

In collaboration with Dr Jeremy Krebs,
Wellington Hospital