Incidence, Prevalence, Natural History and Short-Term Outcomes of NAFLD in First Nations and non-First Nations Community-Based Populations in Manitoba *(The Ookwin Study):*

Current Updates and Preliminary Results

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TRADITIONAL TERRITORIES ACKNOWLEDGEMENT

The University of Manitoba campuses are located on original lands of Anishinaabeg, Cree, Oji-Cree, Dakota, and Dene peoples, and on the homeland of the Métis Nation.

We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of reconciliation and collaboration.

Presentation outline

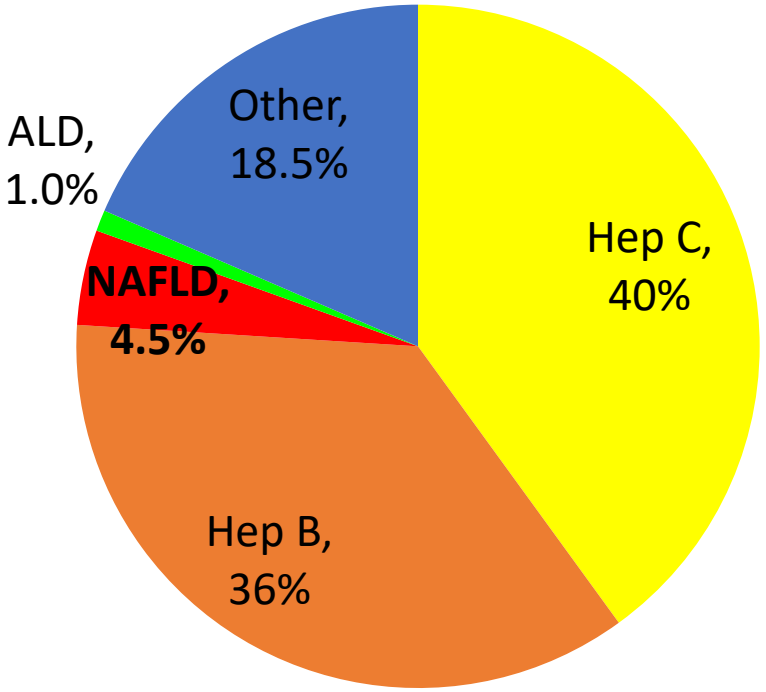
- Introduction
- Study Population
  - Recruitment
  - NAFLD Prevalence
  - Physical/Laboratory profile
- Study updates
- Completed Follow-Up
  - NAFLD Incidence
  - NAFLD Prevalence
  - Physical/Laboratory profile
- Med. Students' Research Projects
- Traditional Diet and Inflammation

What we needed to learn form the study

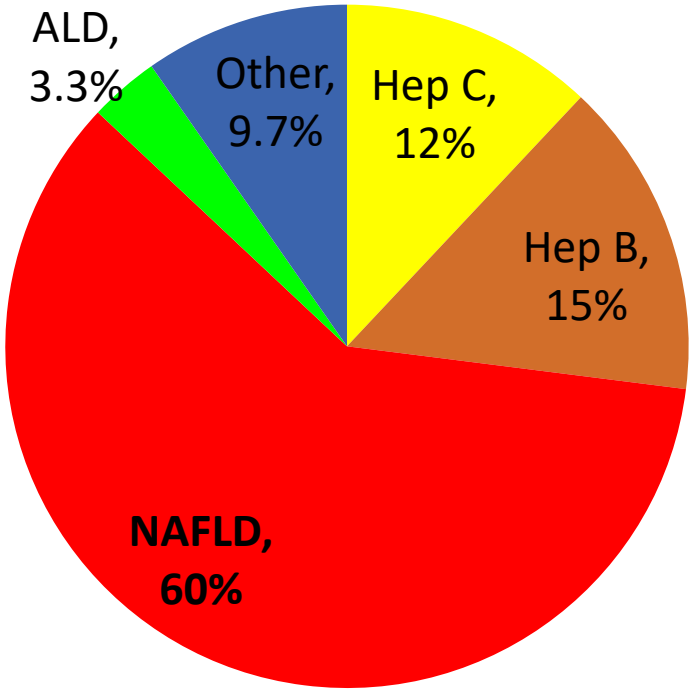
- To find out how common is NAFLD (the Prevalence) within community-based Indigenous and non-Indigenous populations
- To learn how severe is the NAFLD within community-based Indigenous and non-Indigenous populations
- To compare how the NAFLD progress or regress (the Natural History) within Community-Based Indigenous and non-Indigenous Populations
- To find out how many new cases of NAFLD (the Incidence Rates) will develop in 5 years in those who did not have NAFLD on the first visit
- Developing educational and interventional resources about NAFLD and sustainable community programs for participating communities

Changing Trends in Referrals of new patients to HSC hepatology clinics, 1992 - 2017

1992



2017



Referral Dx:	Hep C	Hep B	NAFLD	ALD	Other
Fold change	-3.3	-2.4	**+13.3**	**+3.3**	-1.9

Study Name and Logo

Left to right: Dr. David Miles, Larry Wood, Dr. Gerald Minuk, Dr. Julia Uhanova, Kian Harper, Wallace McDougall, Raquel Koenig, Byron Beardy

The first study team and a Logo Contest Winner **Kian Harper** from Wasagamack

***"Ookwin"* means "*Liver*" in Anisininew language**


Study Participants
2018-2024
10 30 2017

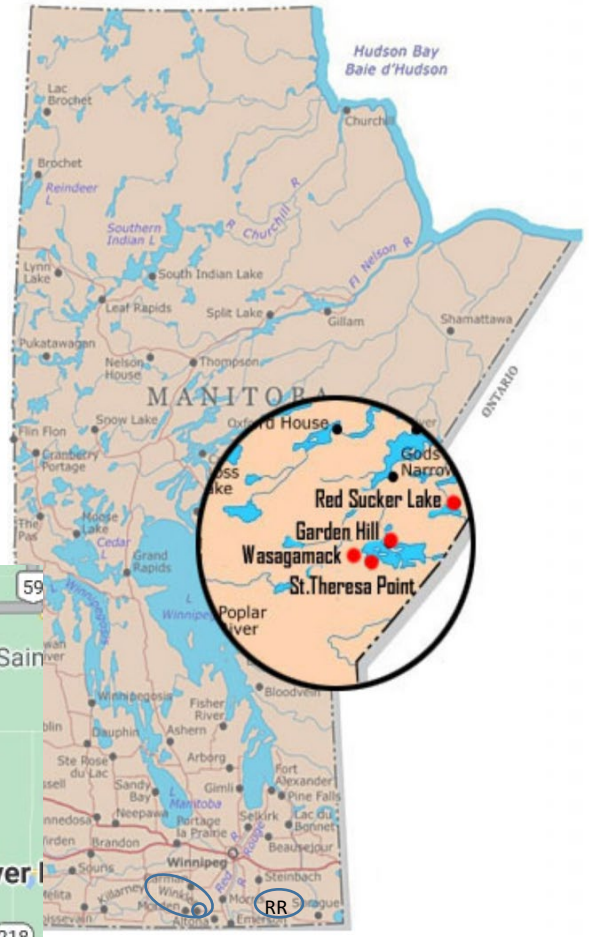
Total Recruitment

Community	Recruited	Target	% of target
Indigenous	967	1,000	96.7
Winkler	900	1,000	90.0
TOTAL	1,867	2,000	**93.4**

Participating Communities

Manitoba:

Population	~1,320,343
Median Age	38.1
Indigenous	15%
Median Age	25.7



<u>Population ~8,809. Median age 19.4 yrs.</u>

Garden Hill	3,553 (20.1 yrs.)
St Theresa Point	3,019 (18.8 yrs.)
Red Sucker Lake	814 (23.4 yrs.)
Wasagamack	1,423 (19.4 yrs.)

Roseau River: <u>Population 564. Median age 23.6 yrs.</u>

Winkler: <u>Population 9,110. Median age 34.8 yrs.</u>

Recruitment , Island Lake and Roseau River

Community	Recruited	%
Garden Hill	210	24.8
Red Sucker Lake	194	22.9
St Theresa Point	183	21.6
Wasagamack	167	19.7
Urban Island Lake	92	10.9
Total Island Lake	846/967	87.5
Roseau River	121/967	12.5
TOTALS	967	

Recruitment , Winkler and Area

Community	Recruited	%
Winkler	583	64. 8
Morden	168	18. 7
Altona	36	4.0
Other towns	113	12.6
TOTALS	900	

Recruitment and Current Status (as of Sept. 2024)

Community	Enrolled	Died/Moved/ Opted out	Final Visit Completed	Remains to be seen
Garden Hill	210	9	72	129 (61.4)
Red Sucker Lake	194	16	123	55 (28.3)
St Theresa Point	183	15	71	97 (53.0)
Wasagamack	167	9	113	45 (26.9)
Urban Island Lake	92	5	22	65 (70.6)
Roseau River	121	7	0	114 (94.2)
Winkler and area	900	102	376	422 (46.8)
TOTALS	1,867	75 (4.0)	777 (41.6)	1,015 (54.4)

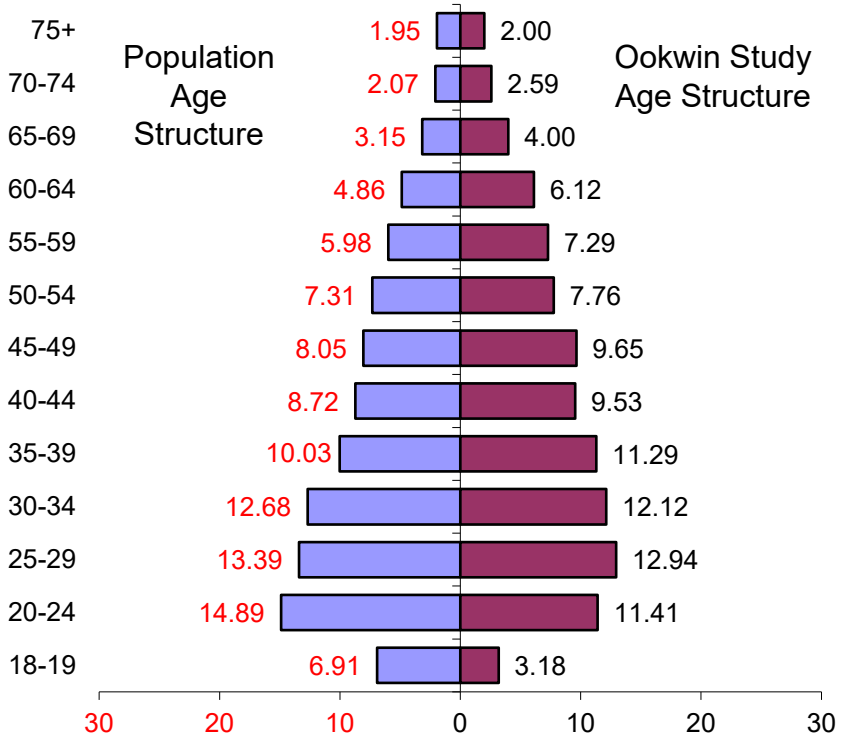
Demographics

	Indigenous (N=967)		Caucasian (N=900)		Total (N=1,867)	
Female	55.1%	533	66.7%	600	60.7%	1,133
Female/Male Ratio	1.23		2.00		1.54	
Mean Age (Median)*	42±15	(40)	53±15	(55)	47±16	(48)
Mean Age, Females	43±15	(41)	53±14	(54)	48±16	(49)
Mean Age, Males	41±15	(39)	53±16	(55)	46±17	(45)

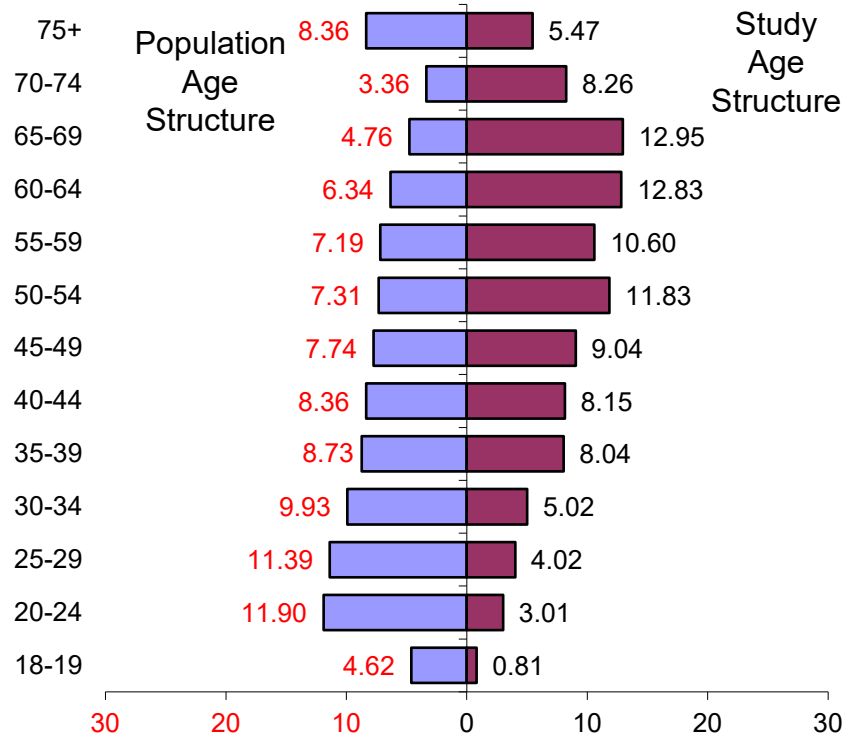
*Age at initial visit

Study Demographics

Island Lake

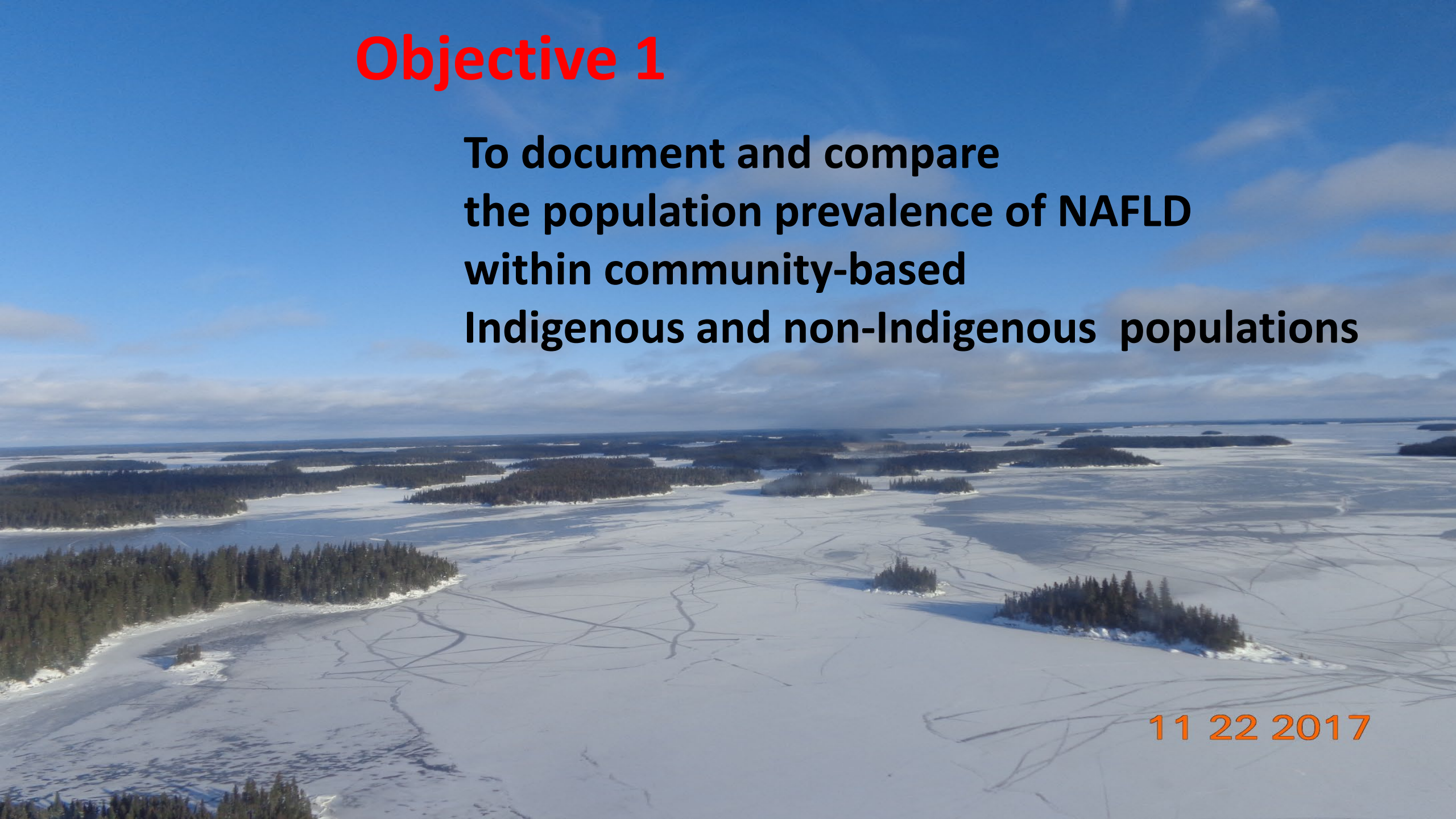


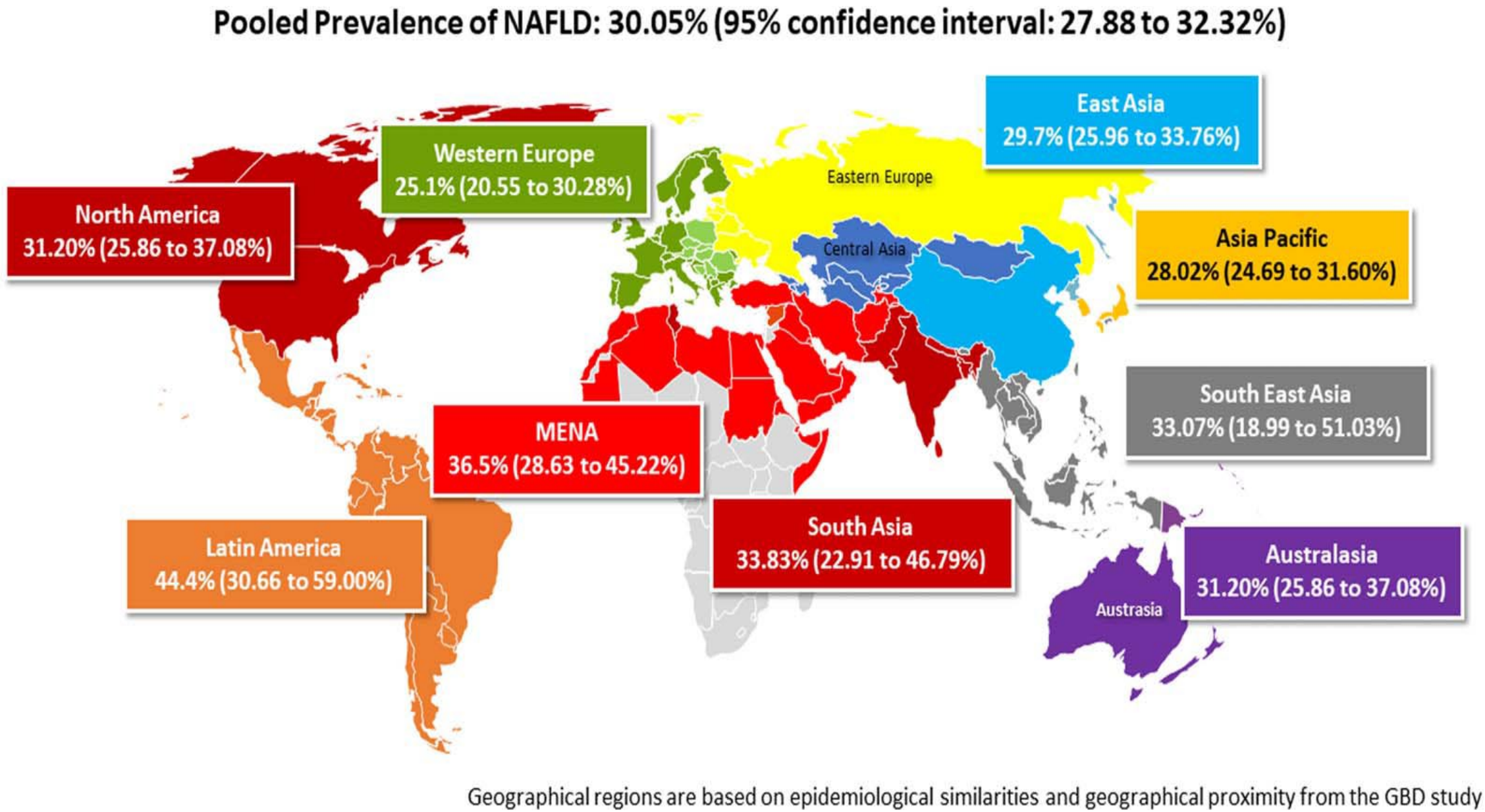
Winkler



Objective 1

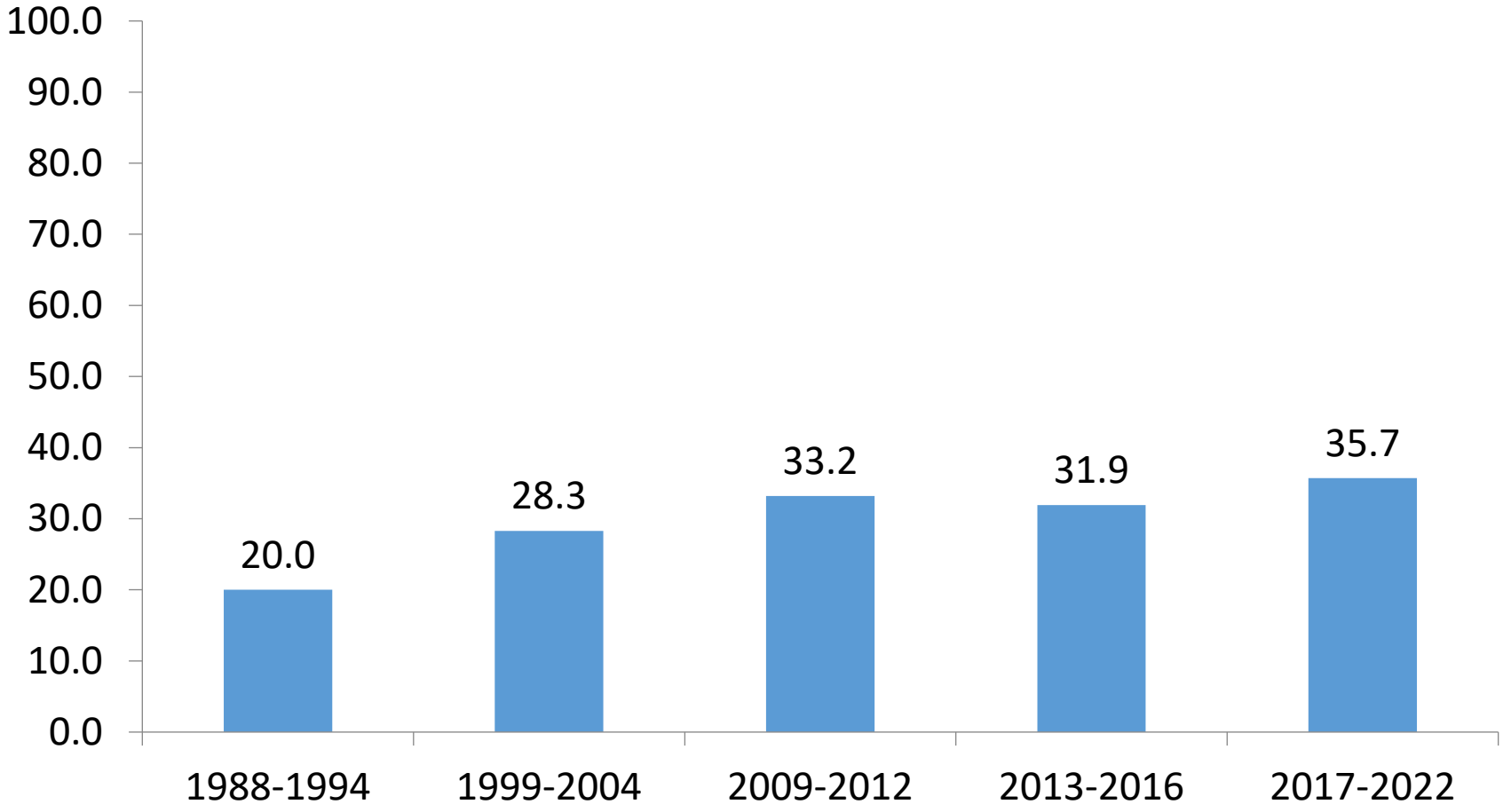
To document and compare the population prevalence of NAFLD within community-based Indigenous and non-Indigenous populations





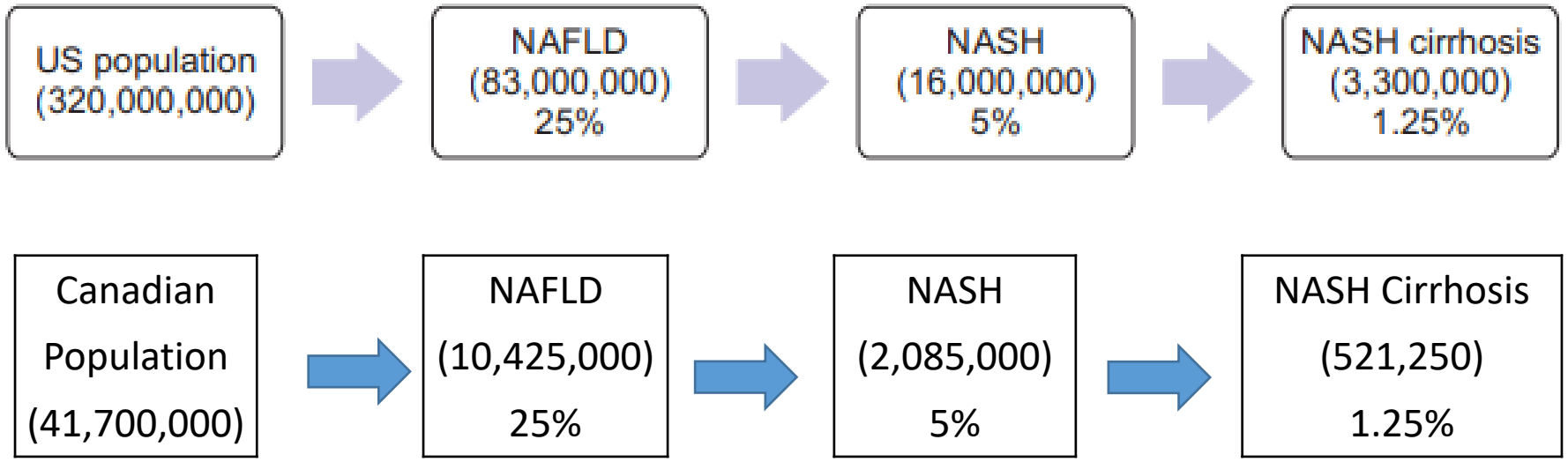
Z. M. Younossi et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77:1335–1347

Prevalence of NAFLD on national health and nutrition surveys (NHANES), USA



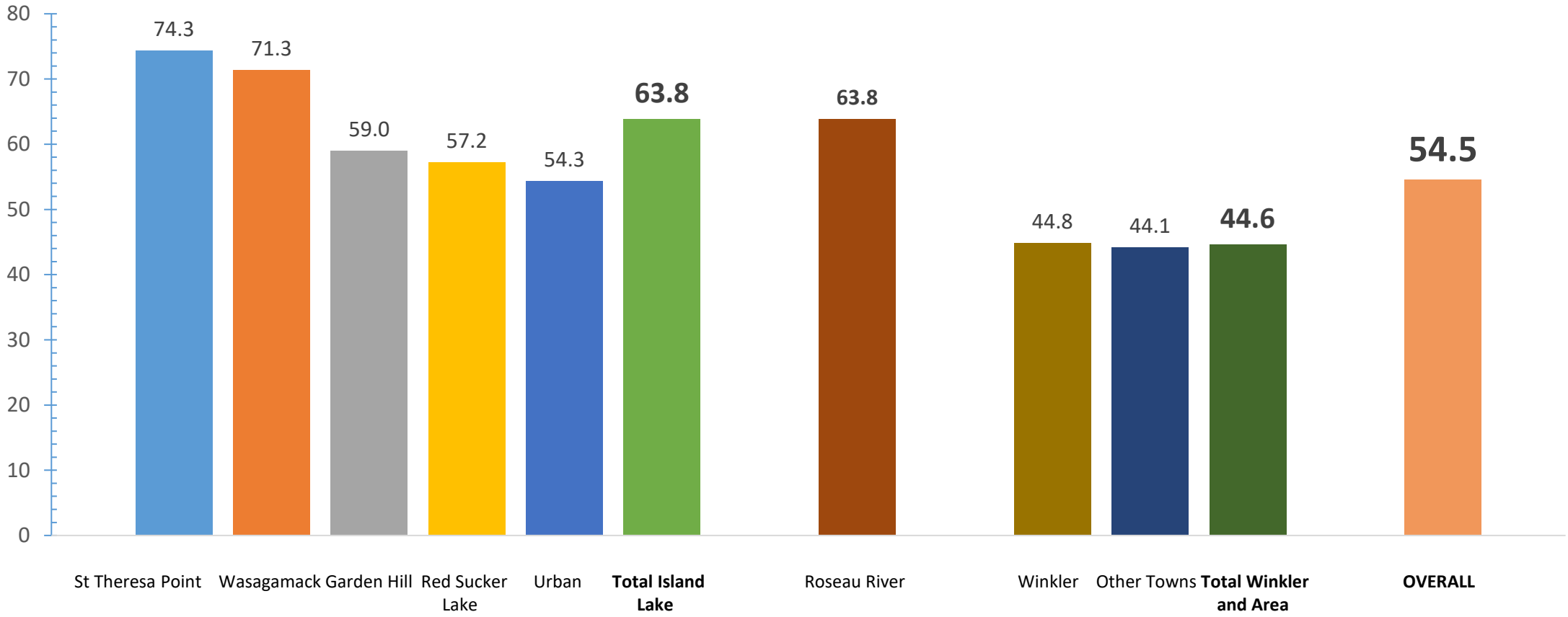
N. Luo et al. Prevalence of steatotic liver disease and associated fibrosis in the United States: Results from NHANES 2017-March 2020. J Hep, 2024.

Estimated number of individuals affected by NAFLD in the USA and Canada



USA Data: S Murag et al. Recent Epidemiology of Nonalcoholic Fatty Liver Disease. Gut Liver 2021;15:206-216
Canadian data: calculated using Canada's population clock (real-time model), https://www150.statcan.gc.ca/n1/pub/71-607-x/71-607-x2018005-eng.htm

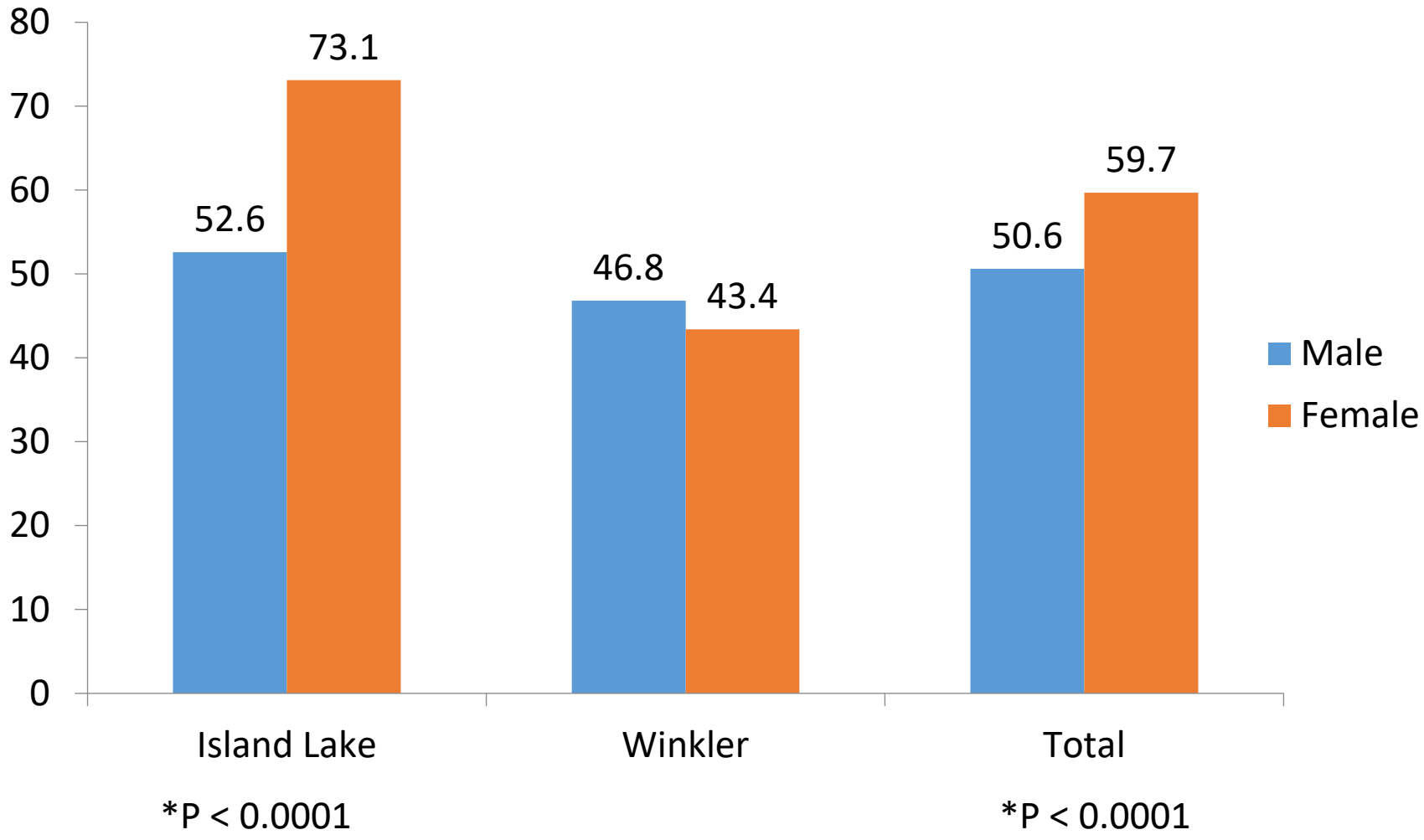
Prevalence of Hepatic Steatosis on ultrasound



Demographics

	First Nations (N=967)		Non-First Nations (N=900)		Total (N=1,867)	
	NAFLD	No NAFLD	NAFLD	No NAFLD	NAFLD	No NAFLD
N (%)	617 (63.8)	350 (36.2)	401 (44.6)	499 (55.4)	1,018 (54.5)	849 (45.5)
Female, %	61.8%	43.4%	65.3%	67.7%	63.2%	57.7%
Female/Male Ratio	1.61	0.77	1.88	2.10	1.71	1.36
Age, Mean (Median)	44.8 (44)	36.7 (33)	55.4 (57)	51.5 (53)	49.0 (50)	45.4 (44)
Age F, Mean (Median)	44.7 (43)	38.1 (35)	55.1 (56)	51.6 (53)	49.0 (49)	47.4 (46)
Age M, Mean (Median)	44.8 (44)	34.7 (32)	55.9 (58)	51.2 (51)	48.9 (51)	42.6 (38)

Prevalence of Hepatic Steatosis on ultrasound



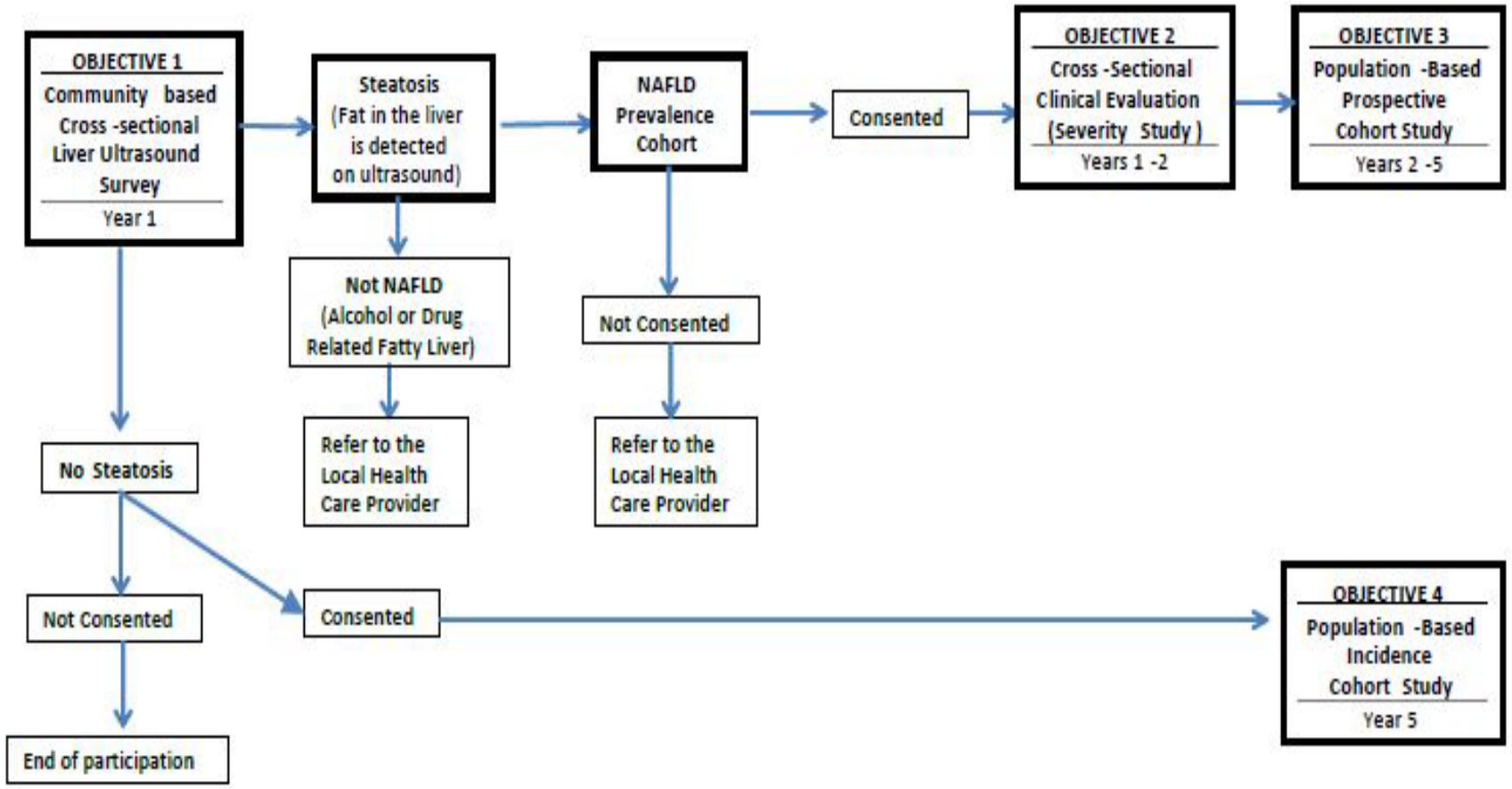
Objective 2

To document and compare the severity of NAFLD within community-based Indigenous and non-Indigenous populations

https://www.youtube.com/watch?v=FRmmehS0qL0

11 22 2017

Study Flow Chart



Objective 5: increasing community awareness and developing NAFLD educational resources and community intervention strategies

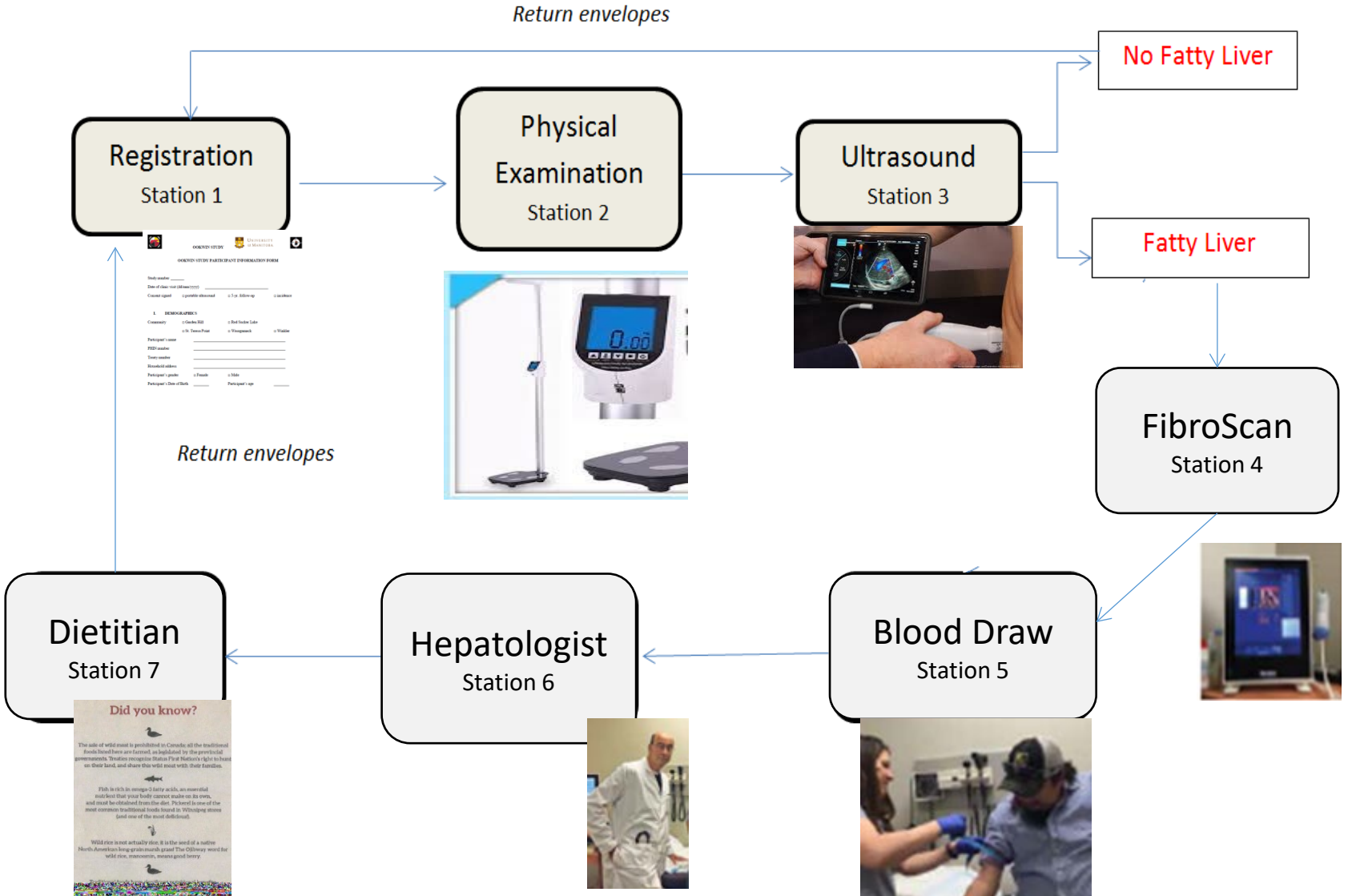
NAFLD Study Clinics Stats, 2018-2024 (as of August 2024)

• Participant encounters		4,677 (935.4/yr.)
• Total Clinics		189
Island Lake	61	
Winkler	102	
Urban	14	
Roseau River	9	
• Baseline visits		1,876
• *Recruited*		*1,867*
• Follow up visits		2,801
• Final visits		777

NAFLD Study Clinics Stats, 2018-2024 (as of August 2024)

• In-person clinics	126
• Virtual clinics	63
• Virtual follow-up clinic's participants	972
• Average patients per virtual clinic	15.4
• Max. Intake, Island Lake/RSL	148 in 2 days 74/day
• Max. Intake, Winkler Site	57
• Max. Follow-up, Island Lake/RSL	51
• Max. Follow-up, Winkler	44

Ookwin Clinic Flow Chart



Risk Factors for NAFLD

	First Nations (N=967)		Non-First Nations (N=900)		Total (N=1,867)	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
BMI*	31.4±7.1	(30.9)	30.0±6.4	(29.0)	30.6±6.7	(30.0)
<18.5 (low)	0.7%		0.6%		0.66%	
18.5-24.9 (normal weight)	10.2%		15.2%		12.5%	
25.0-29.9 (overweight)	24.3%		31.2%		27.6%	
>30 (obesity)	63.8%		51.9%		58.2%	
HbA1C level*	6.9±2.1	(6.0)	6.0±1.1	(5.7)	6.57±1.9	(5.8)
Diabetes*	32.2%		10.2%		21.5%	
Hypertension	29.2%		28.3%		28.8%	
Dyslipidemia*	20.0%		11.0%		15.6%	
Sleep Apnoea*	4.03%		10.1%		6.9%	
Metabolic Syndrome**	1.65%		0.44%		1.07%	

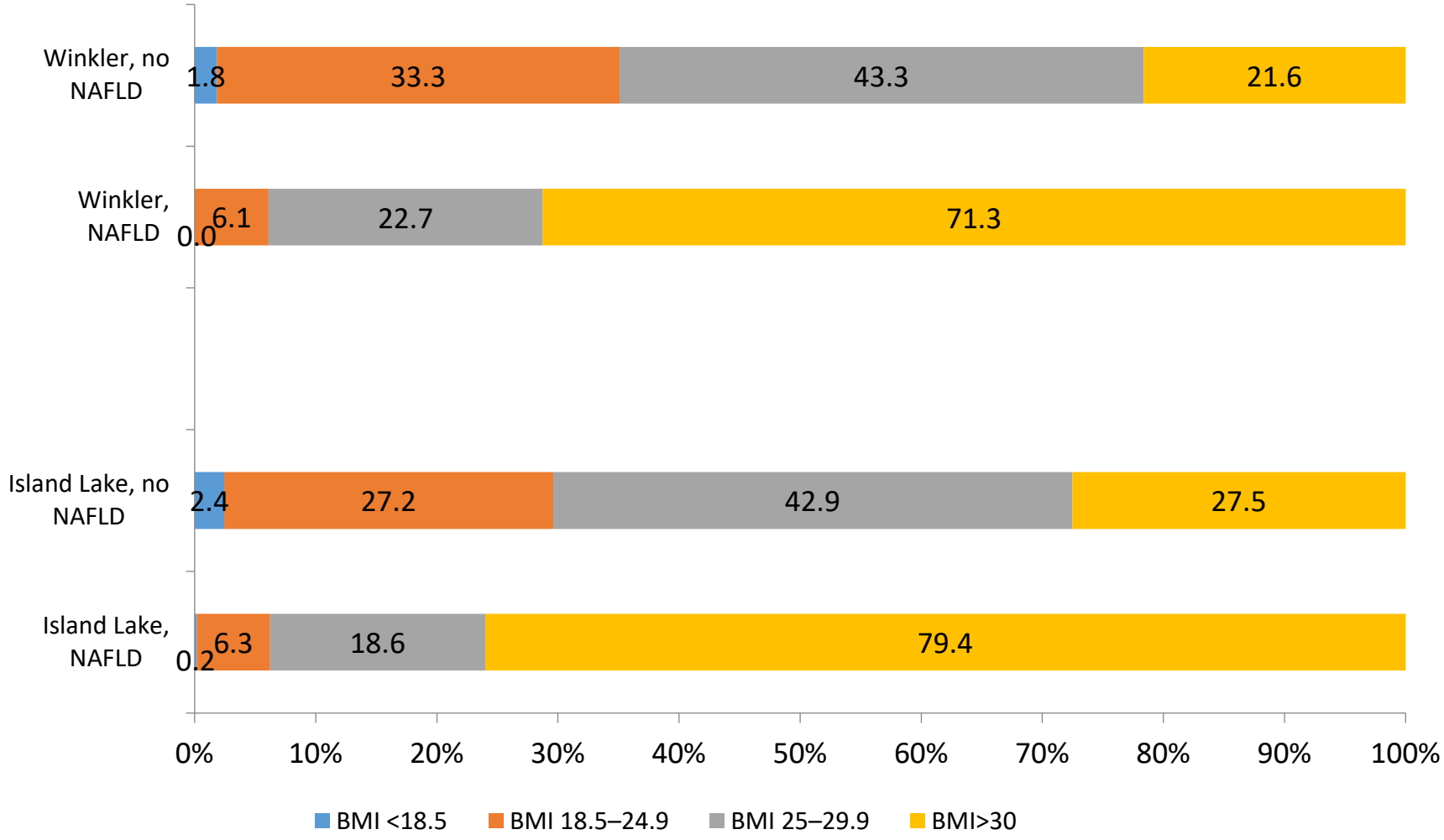
*P<0.0001
**P 0.011

Risk Factors for NAFLD

	NAFLD (N=1,018)		No NAFLD (N=834)		Total (N=1,852)	
	N	%	N	%	N	%
BMI*	33.6±6.6	(33.0)	27.1±4.8	(26.8)	30.6±6.7	(30.0)
<18.5 (low)	24	2.4	34	4.1	61	3.3
18.5-24.9 (normal weight)	64	6.3	248	29.7	313	16.8
25.0-29.9 (overweight)	209	20.5	349	41.9	562	30.1
>30 (obesity)	709	69.7	194	23.3	910	48.7
Diabetes*	290	28.5	110	13.2	400	21.6
Hypertension*	363	35.7	171	20.5	534	28.8
Dyslipidemia	191	18.8	98	11.7	289	15.6
Sleep Apnoea*	94	9.2	36	4.3	130	7.02
Metabolic Syndrome	17	1.67	3	0.36	20	1.08

*$p<0.0001$

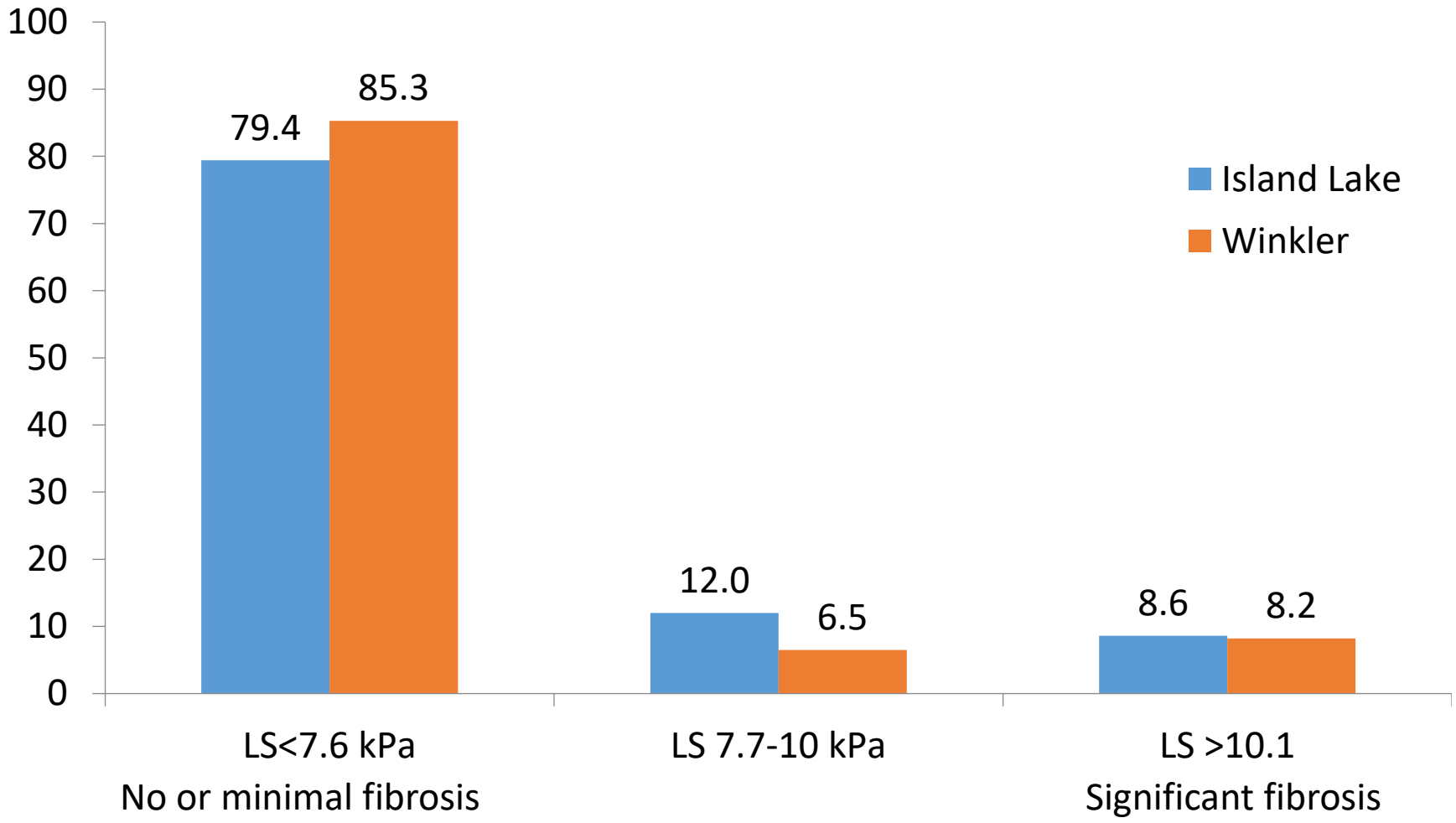
BMI of participants with and without NAFLD



Baseline Laboratory Test Results

	First Nations (N=967)		Non-First Nations (N=900)		P
	Mean±SD	**Median**	**Mean±SD**	**Median**	
Albumin	37.3±4.2	37	44.5±3.9	45	<0.0001
ALT	33.8±30.5	24	28.1±17.1	23	0.171
AST	30.3±27.8	23	23.4±10.5	20	0.0002
AP	108.2±32.5	104	77.6±22.5	77	<0.0001
Bilirubin Total	6.2±3.7	5.0	8.0±3.8	7.0	<0.0001
Bilirubin Direct	2.4±0.8	2.0	2.8±1.0	2.0	<0.0001
GGT	49.2±60.7	32	36.2±41.1	23	<0.0001
INR	1.0±0.6	1.0	1.0±0.2	1.0	0.002
Haemoglobin	135.6±17.5	137	140.2±12.4	141	0.0001
Platelets	311.1±76.3	304	264.3±145.7	247.5	<0.0001
T. Cholesterol	3.6±1.3	3.6	3.9±1.1	3.9	<0.0001
Triglycerides	2.1±1.5	1.7	2.0±1.3	1.66	0.110

Liver Stiffness



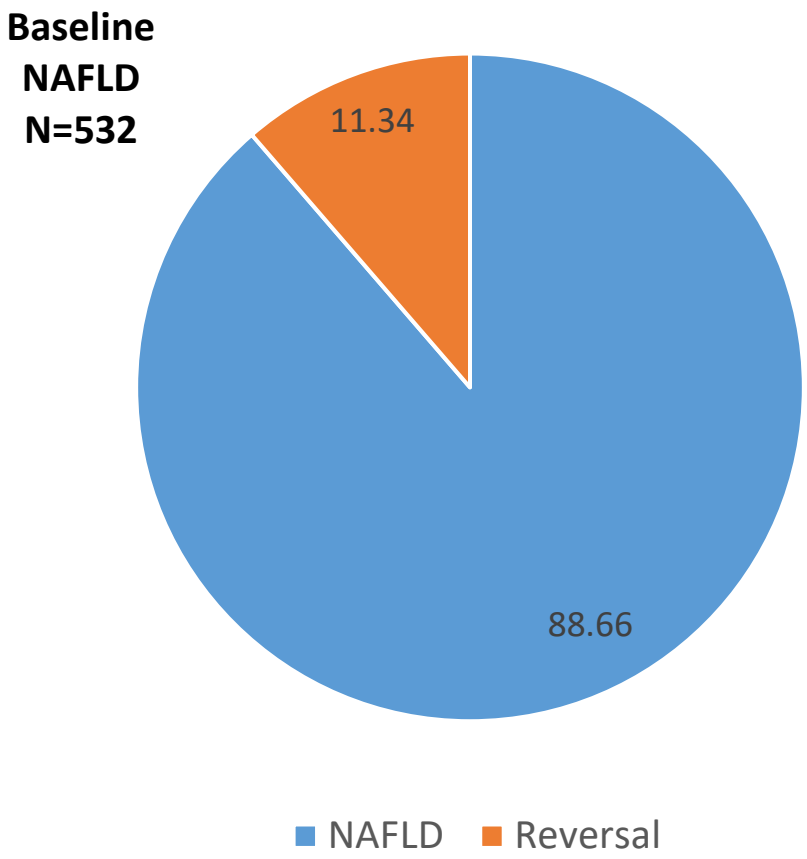
Objective 3

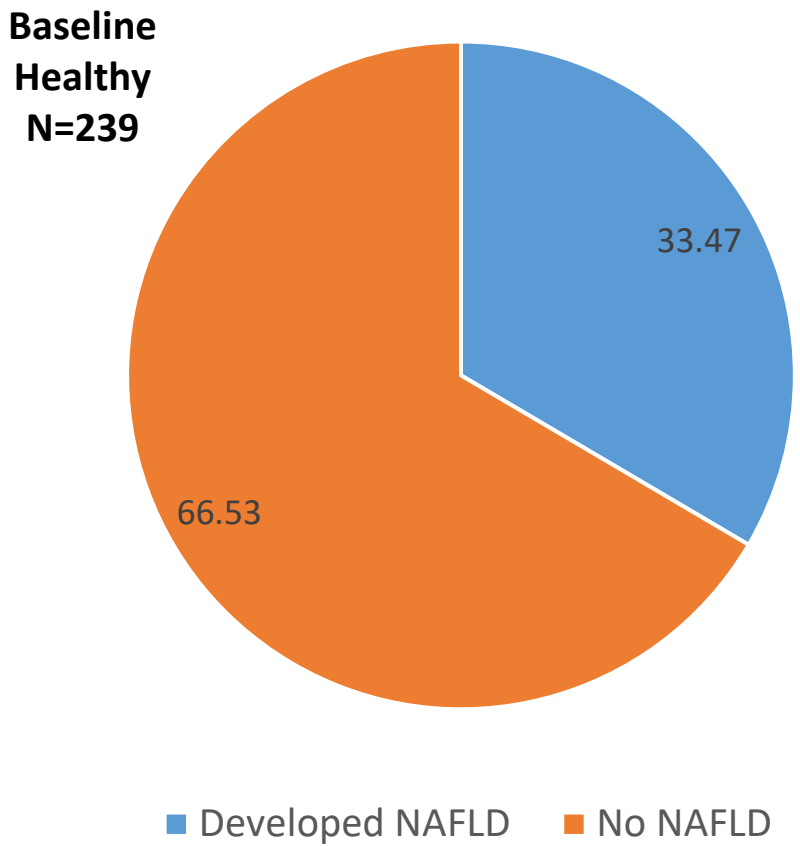
To Document and Compare the Natural History of NAFLD within Community-Based Indigenous and non-Indigenous Populations

Reversal of NAFLD

	Final visit steatosis	Final visit no steatosis	Total
Baseline steatosis	474 (89%)	**58 (11%)**	532
Baseline no steatosis	**79 (33%)**	160 (67%)	239
Total	553	218	771

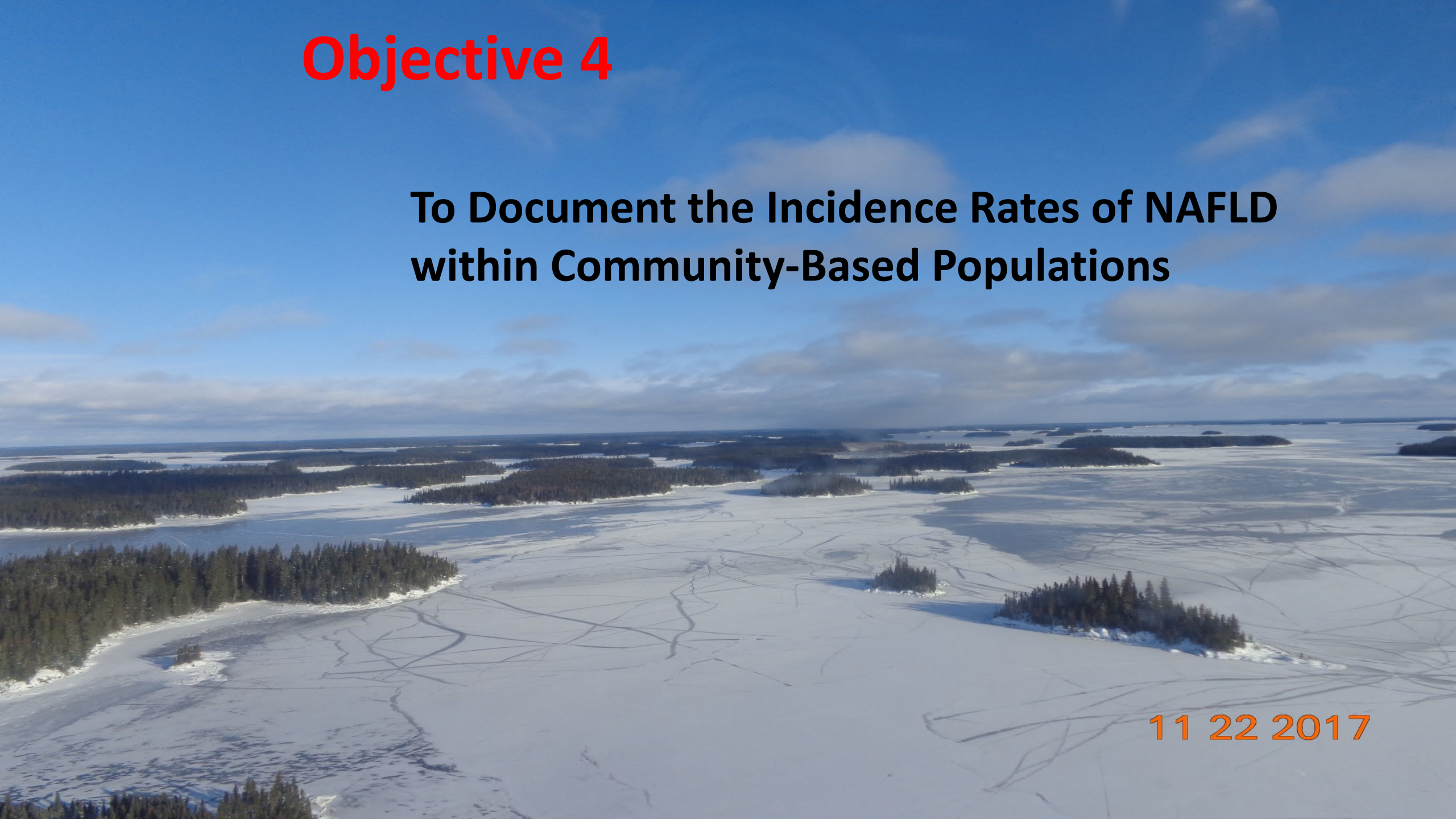
Change in NAFLD status (N=771)





Objective 4

To Document the Incidence Rates of NAFLD within Community-Based Populations



Incidence Rates of NAFLD by Country

	Studies	Rate per 1000 person/yrs. (95%CI)	I^2 (heterogeneity)
Total	12	48.89 (38.49–61.93)	99.70
Country			
China	6	50.69 (35.05–72.77)	99.45
Germany	1	32.54 (30.08–35.18)	
Japan	1	27.02 (25.88–28.20)	
South Korea	3	53.98 (41.19–70.44)	98.55
Sri Lanka	1	79.29 (71.55–87.79)	

Z. M. Younossi et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77:1335–1347

Incidence of new steatosis in Ookwin study in a subset of 777 completed records

	N	5-yr cumulative incidence	Incidence rate
Initially Healthy participants	239		
Developed NAFLD	79		
Person/years	1159		
Incidence		330.5 per 1,000 pop.	68.16 per 1,000 P/Yrs.

Incidence Rates of NAFLD by Country

	Studies	Rate per 1,000 person/yrs. (95%CI)	I^2 (heterogeneity)
Total	12	48.89 (38.49–61.93)	99.70
NAFLD Ookwin	1	**68.16** (53.96–84.95)	
China	6	50.69 (35.05–72.77)	99.45
Germany	1	32.54 (30.08–35.18)	
Japan	1	27.02 (25.88–28.20)	
South Korea	3	53.98 (41.19–70.44)	98.55
Sri Lanka	1	79.29 (71.55–87.79)	

Objective 5

Developing educational and interventional resources about NAFLD and sustainable community programs for participating communities

Alaska Native saying

“Researchers are like mosquitoes; they suck your blood and leave.”

P.A.L. Cochran at al. Indigenous Ways of Knowing: Implications for Participatory Research and Community. Am J Public Health. 98:22-27.

Community Based Projects

Approaching Non-Alcoholic Fatty Liver Disease Through Nutrition and Physical Activity from an Indigenous Perspective

- Conducting environmental scan of existing programs and resources
- Conducting interviews with the Four Arrows RHA program staff and community members
- Identifying barriers to programming
- Developing goals for sustainable community-based nutrition and exercise program

    - **Red Sucker Lake**
    - **Sydnee Tuckett, Med II summer research project**
    - **Summer 2019**

Community Based Projects

Does gardening protect against NAFLD?

- Assessing the association between gardening and NAFLD using dataset collected from adults living in or near Winkler, Manitoba (n=302)
- Conducting interviews with 23 gardeners to determine the intensity of their gardening activities and reasons for gardening among participants in NAFLD follow-up clinics

    - **Winkler, MB**
    - **Grace McEwen, Med II summer placement project**
    - **Summer 2019**

Community Based Projects

Paving the Way to Community –specific intervention and prevention strategies for NAFLD in Indigenous Communities

- Questionnaires and semi-structured interview interviews to assess the diet and lifestyles of participants **with** and **without** NAFLD
- Exploring how community members define and understand NAFLD
- Exploring the perceptions and experiences of community members regarding health and well-being, including diet, physical activity and cultural connectedness
- Examining determinants of everyday lifestyle choices and perceived barriers to health and wellbeing.
- Investigating perceived opportunities that would promote education and prevention of NAFLD.
    - **St Theresa Point**
    - **Diana Craig, BSc. Med project, 2019-2020**

Community Based Projects

Understanding Barriers to Adherence to Traditional Indigenous Diet for Individuals with Non-Alcoholic Fatty Liver Disease

- Conducting qualitative study of 20 in-depth interviews
- Perform thematic content and narrative analysis of transcripts
- Explore the motivating factors that promote adherence to traditional Indigenous diet
- Explore the barriers that prevent adherence to traditional Indigenous diet

  - **Garden Hill, Wasagamack**
  - **Tristan Rohatynsky, Med I summer research project**
  - **Summer 2023**

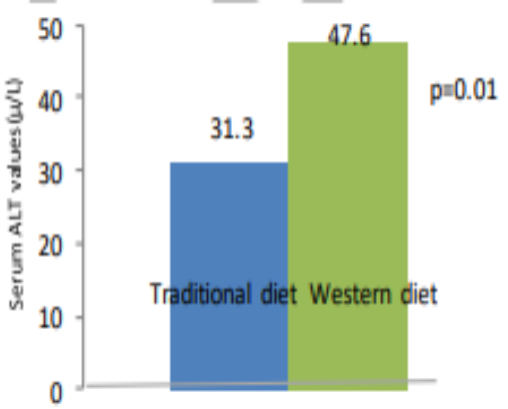
Community Based Projects

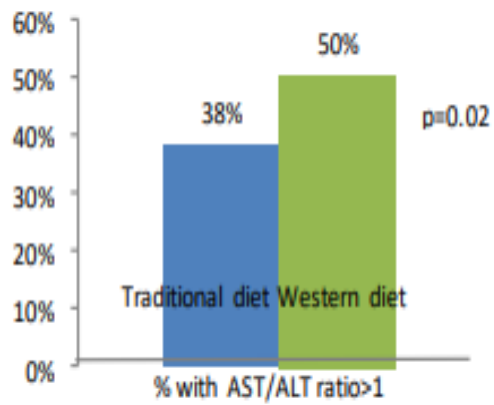
Reversal of NAFLD Amongst Residents in Remote First Nations Communities: A Qualitative Analysis

- Study goal: to increase understanding of factors that promote and hinder reversal of NAFLD specifically within Island Lake Communities
- Performed interviews with study participants who reversed NAFLD since 2018 and age, gender, and community-matched group of those who did not
- Performed thematic content analysis of transcripts
- Identifying trends that are widely applicable amongst community members

    - **Red Sucker Lake, St. Theresa Point**
    - **Gagan Mavi, Med II summer research project**
    - **Summer 2023**

Traditional Indigenous Land-Based Diet and Chronic Inflammation: Does Adherence to the Traditional First Nations Diet Decrease the Severity of Chronic Inflammatory Diseases?





Aims and Objectives

1) To determine whether if NASH is less common in those who consume mainly Traditional versus Western diets.

2) To document the correlation between self-reported dietary intake and stable isotope analysis.

3) To determine whether consumers of a Traditional diet have lower pro-inflammatory profile than consumers of a Western-style diet.

4) To engage in Indigenous knowledge translation regarding traditional Indigenous food practices.

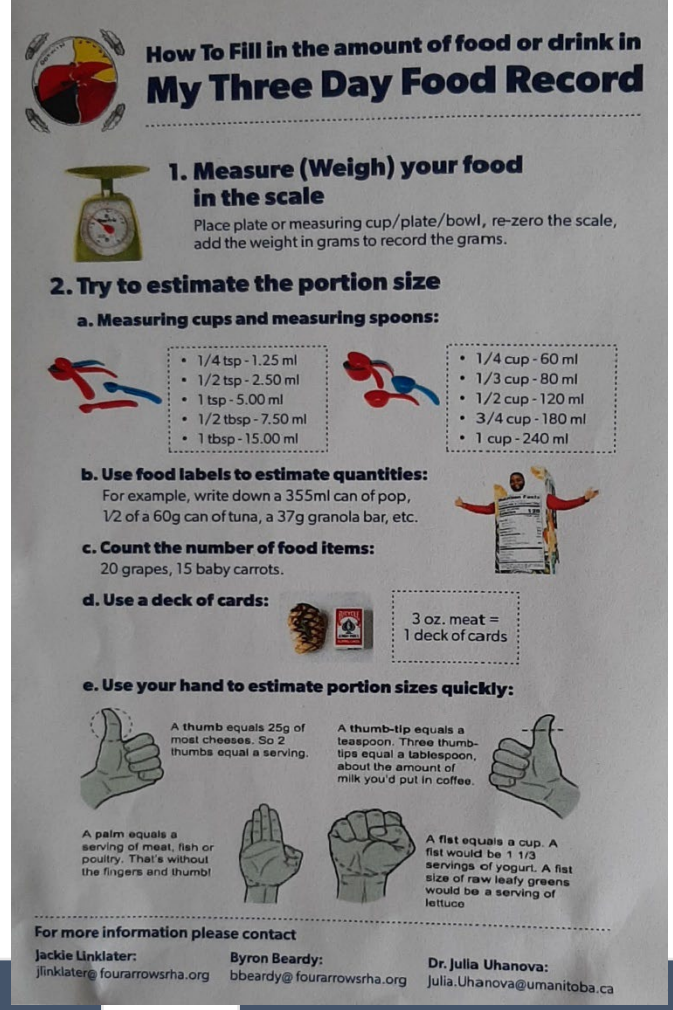
Procedure

Study enrollment

Walkthrough of the study procedure with study staff

Bloodwork, sample collection (hair and blood), medical history and anthropometrics

3-day dietary intake record



How To Fill in the amount of food or drink in
My Three Day Food Record

1. Measure (Weigh) your food in the scale

Place plate or measuring cup/plate/bowl, re-zero the scale, add the weight in grams to record the grams.

2. Try to estimate the portion size

a. Measuring cups and measuring spoons:

- 1/4 tsp - 1.25 ml
- 1/2 tsp - 2.50 ml
- 1 tsp - 5.00 ml
- 1/2 tbsp - 7.50 ml
- 1 tbsp - 15.00 ml

- 1/4 cup - 60 ml
- 1/3 cup - 80 ml
- 1/2 cup - 120 ml
- 3/4 cup - 180 ml
- 1 cup - 240 ml

b. Use food labels to estimate quantities:
For example, write down a 355ml can of pop, 1/2 of a 60g can of tuna, a 37g granola bar, etc.

c. Count the number of food items:
20 grapes, 15 baby carrots.

d. Use a deck of cards:

3 oz. meat = 1 deck of cards

e. Use your hand to estimate portion sizes quickly:

A thumb equals 25g of most cheeses. So 2 thumbs equal a serving.

A thumb-tip equals a teaspoon. Three thumb-tips equal a tablespoon, about the amount of milk you'd put in coffee.

A palm equals a serving of meat, fish or poultry. That's without the fingers and thumb!

A fist equals a cup. A fist would be 1 1/3 servings of yogurt. A fist size of raw leafy greens would be a serving of lettuce

For more information please contact

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Dr. Julia Uhanova: Julia.Uhanova@umanitoba.ca

Participants are asked to document all food and drinks they consumed in the next 3 days (2 weekdays, 1 weekend).

Time of food intake, meal portions, ingredients, cooking method and food source are recorded in the 3-day food record (3DFR)

Participants have the option to complete the 3DFR with the paper-based record or the Ookwin app (smartphone app)

Recruitment to date (as of August 2024)

Community	Control	NAFLD	NASH	Total
St. Theresa Point	24	22	24	70 (93.3)
Garden Hill	4	14	26	44 (58.7)
Wasagamack	8	13	9	30 (40.0)
Red Sucker Lake	10	13	27	50 (66.7)
Total Recruitment	**46**	**62**	**86**	**194 (64.7)**

Community	Hair samples	Blood samples	3DFR
St. Theresa Point	53	57	23 + 3 (redo)
Garden Hill	44	0	-
Wasagamack	25	25	3
Red Sucker Lake	61	34	14 + 6 (couldn’t locate)

Dietary Inflammatory Index (DII)

- Dietary habits has been linked to systemic inflammation through pro- and anti-inflammatory mechanisms.

- The DII is a tool devised to measure overall diet quality in relation to inflammatory potential.

- Food items are analyzed and converted into a list of 45 food parameters (e.g., carbohydrates, lipids, vitamins, microelements)

Dietary Inflammatory Index (DII)

- Negative values reflect anti-inflammatory dietary habits
  - Diet with low inflammatory potential (e.g., Mediterranean diet, macrobiotic diet) are associated with lower risk of metabolic syndrome
- Positive values indicate pro-inflammatory dietary habits
- Higher DII scores are positively associated with:
  - Greater risk of developing NAFLD
  - Severity of NAFLD
  - Comorbidity of metabolic syndromes
  - Inflammatory markers (e.g., CRP, IL-6)

Each food parameter is given a specific weight according to its inflammatory potential.

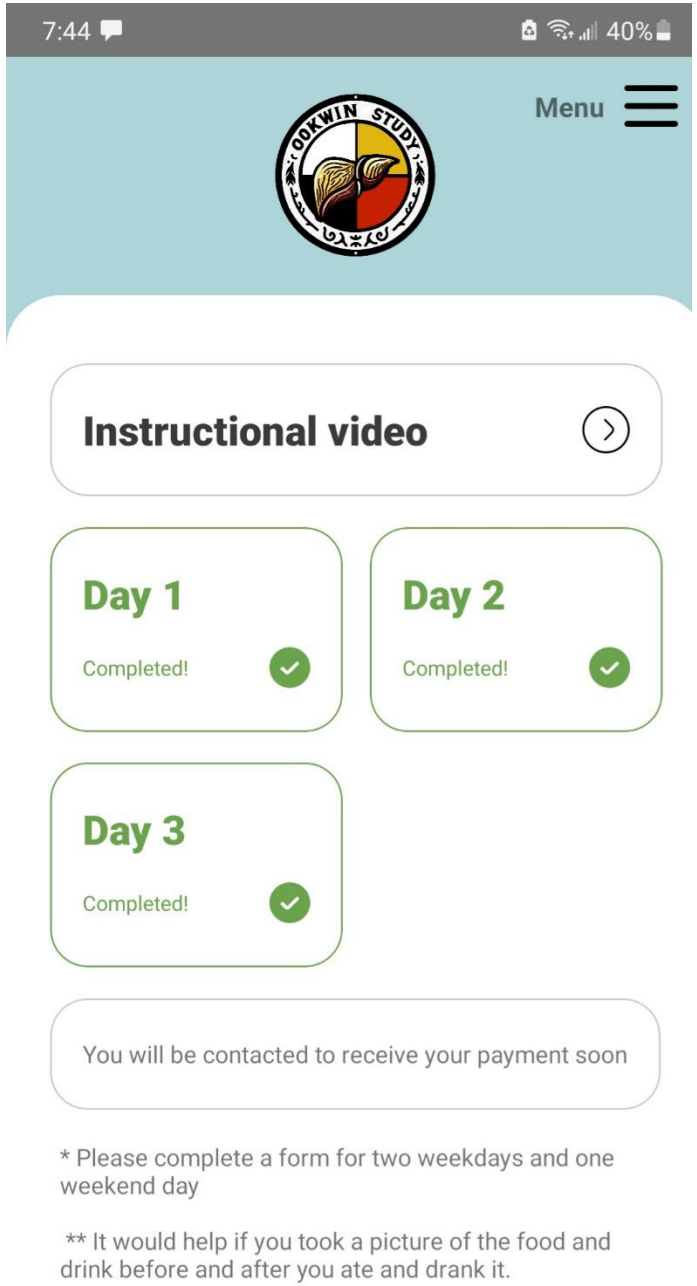
Overall DII score is calculated by summing up the 45 food parameters

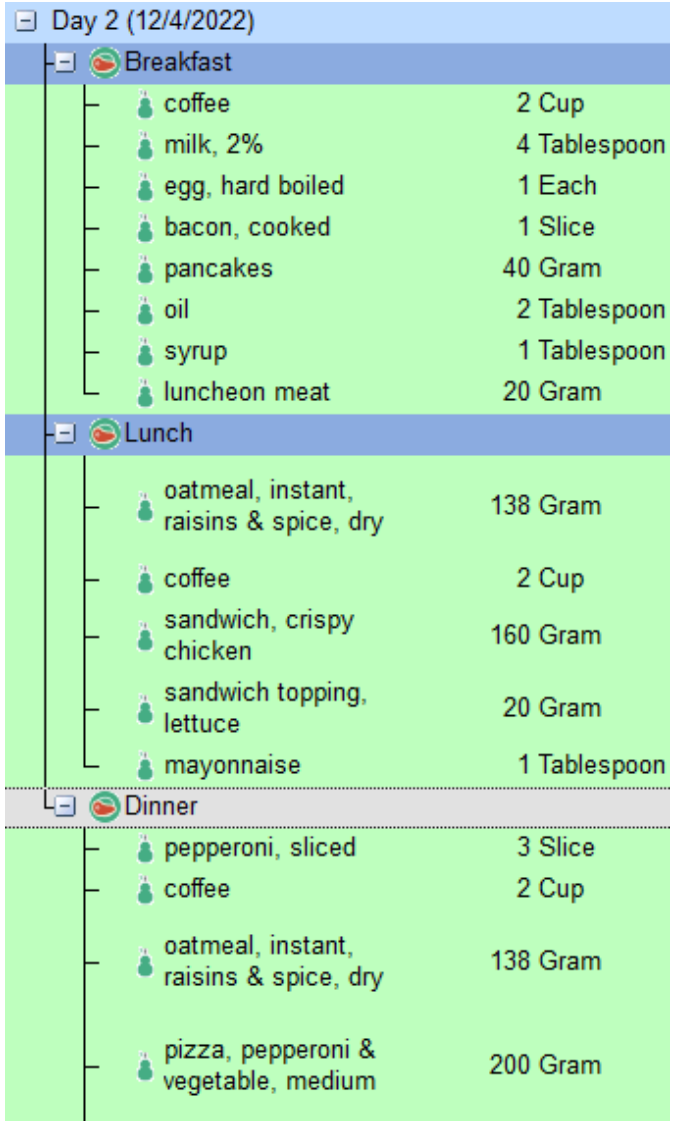
DII scores Max. range	−8.87 to +7.98
Usual range from 25–30 food parameters	−5.5 to +5.5.

The DII has been extensively studied and validated across different kinds of metabolic syndrome components (e.g., obesity, diabetes, NAFLD) as well as other conditions

Calculation of the DII

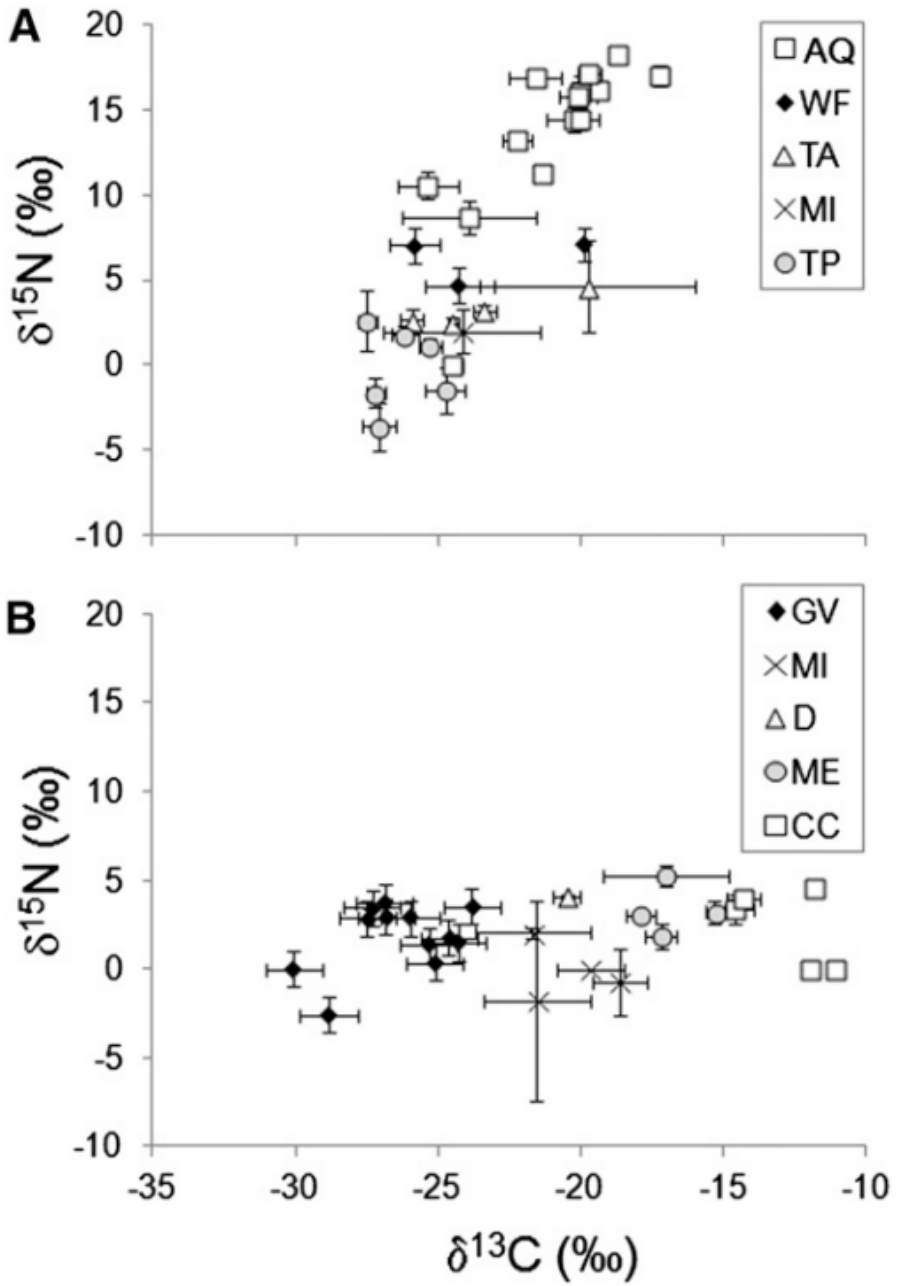
- Completed food records are entered into the ESHA food processor software.
- Food parameters output are generated by the ESHA software

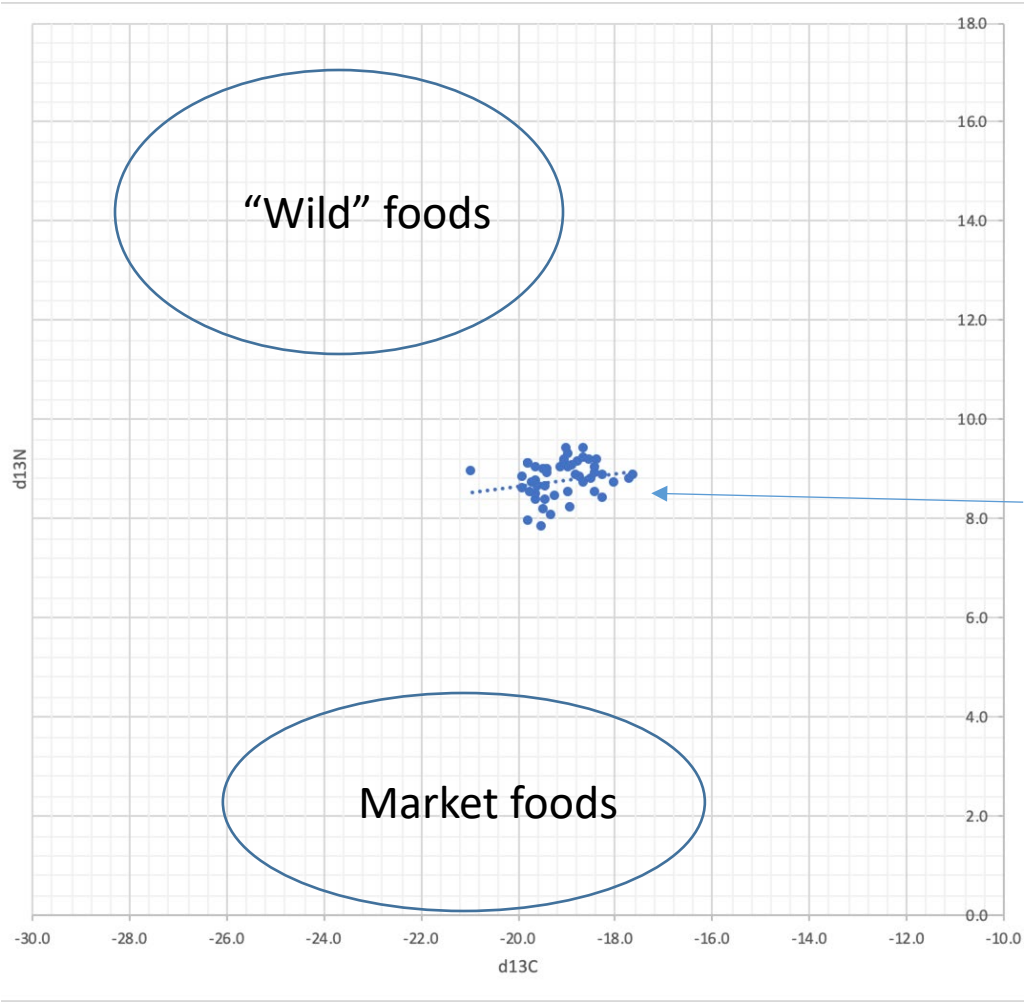




Isotope analysis

- Hair samples will be used for isotope analysis
- Isotope analysis have been used in studies of archaeology and anthropology.
- By examining Carbon and Nitrogen isotope ratios, we can examine food sources and dietary habits
- Hair will be analyzed to assess the contributions of traditional and western foods
- Traditional foods (e.g. aquatic, waterfowl, terrestrial animals and plants) have high 15N /low 13C ratios
- Market foods (e.g. corn and cane sugars, meat, dairy, grains and vegetables) have higher 13C /lower 15N ratios





Hair samples from Island Lake participants

AQ, aquatic; WF, waterfowl; TA, terrestrial animals; MI, mixed; TP, terrestrial plants

GV, grains and vegetables; D, dairy; ME, nontraditional meats; CC, corn and cane sugar based

S.H. Nash et al. Stable Nitrogen and Carbon Isotope Ratios Indicate Traditional and Market Food Intake in an Indigenous Circumpolar Population. J. Nutr.;1012:142: 84–90.

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