Liver Disease in Type 2 Diabetes – Lessons from the Edinburgh Type 2 Diabetes Study

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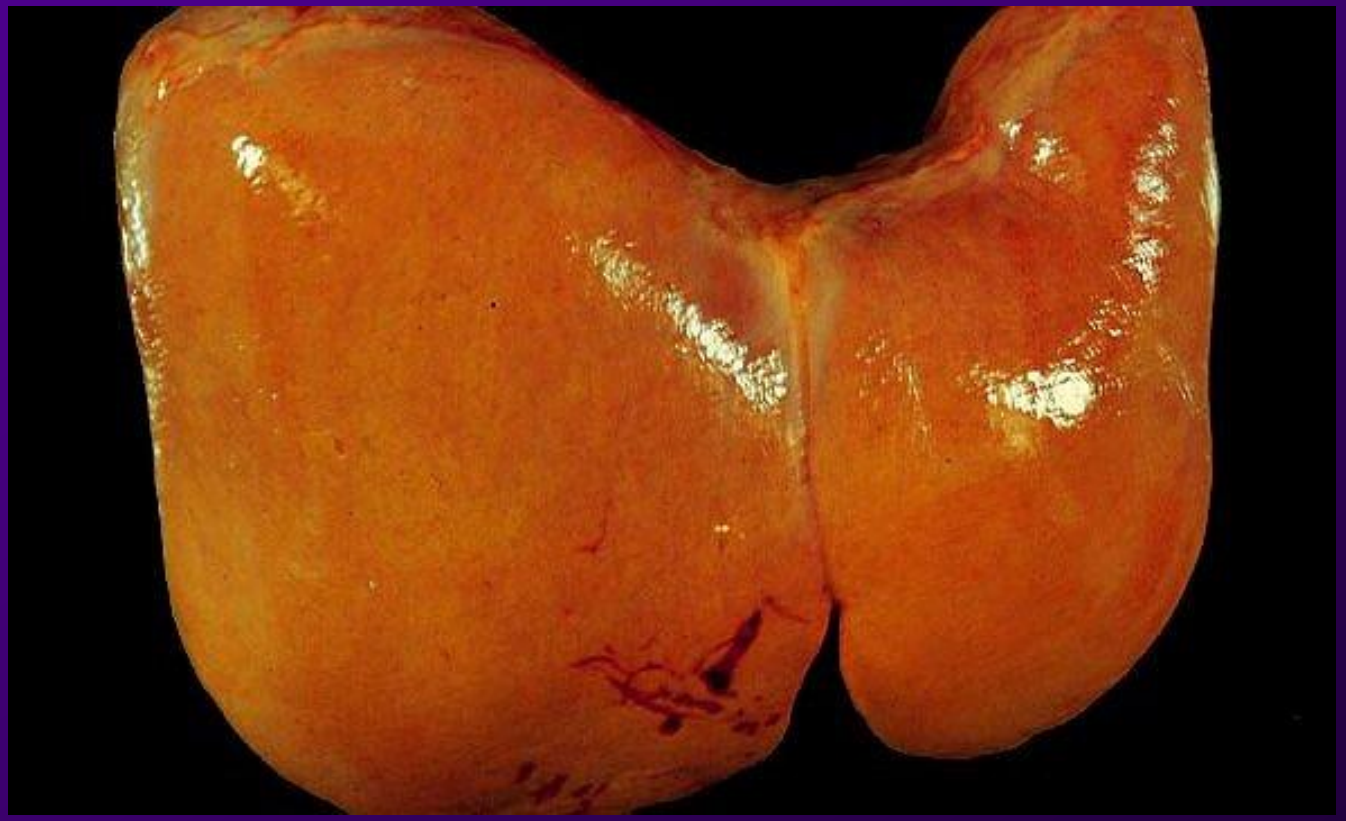
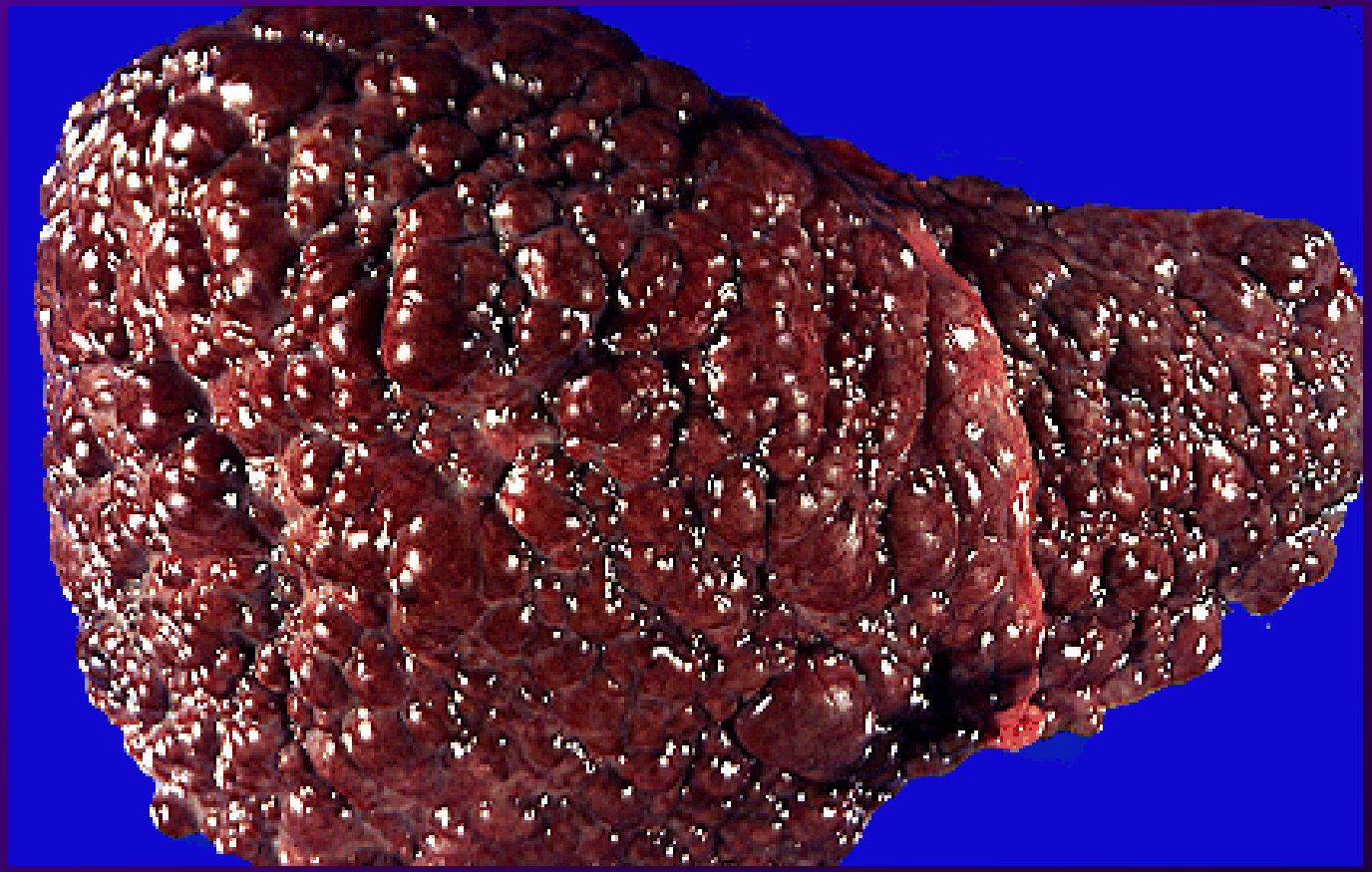
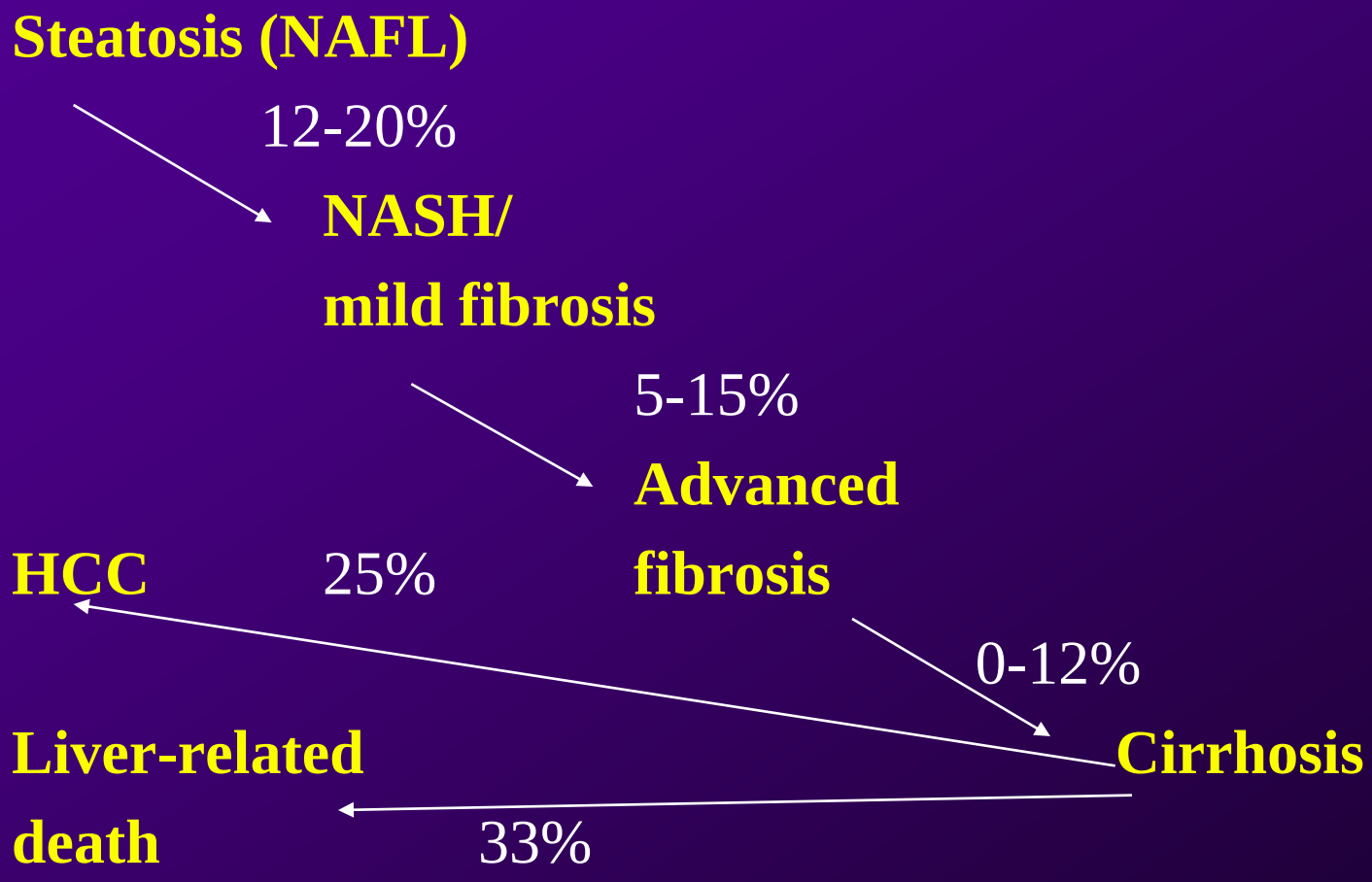
Liver Disease in Diabetes



Liver Disease in Diabetes



Natural History of NAFLD



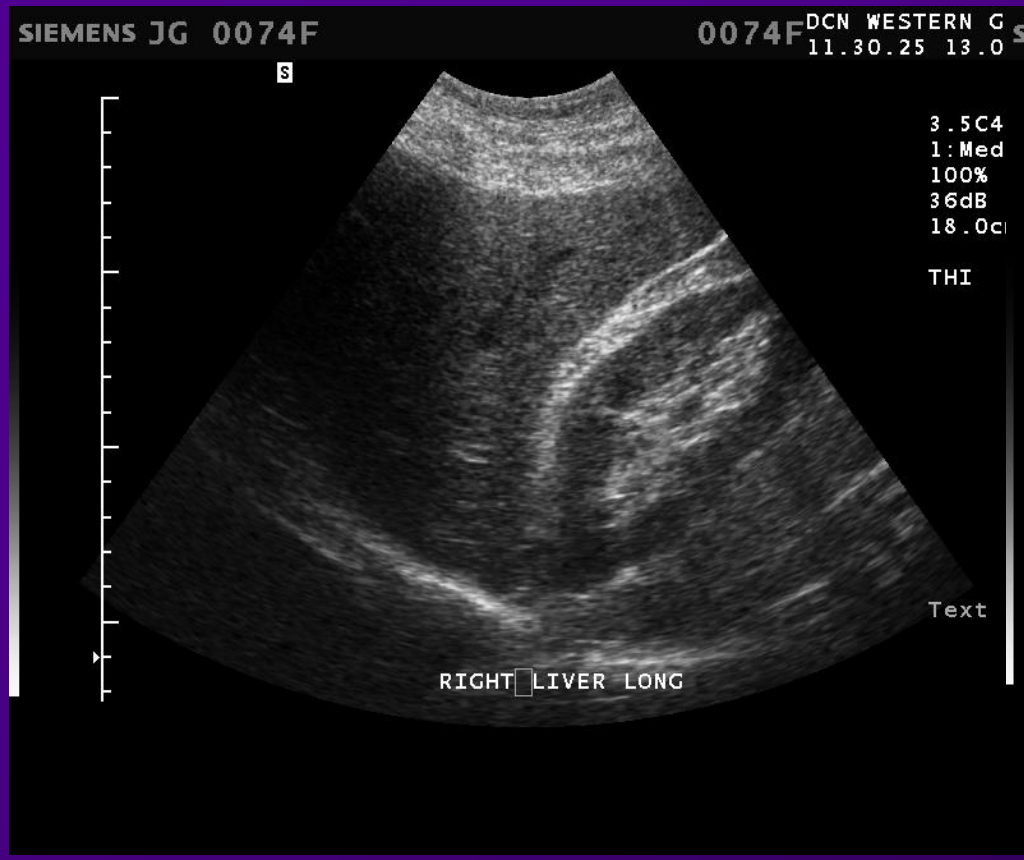
Day, Clinical Medicine, 2006

ET2DS – Main Aim

- To examine the relative effects of potentially modifiable risk factors on cognitive impairment in adults with Type 2 diabetes:
  - Microvascular disease
  - Inflammatory markers
  - HPA axis activity

Liver Disease in the ET2DS

- 939 ET2DS participants were scanned over 12 months
- Dedicated ultrasound scanner
- Dedicated ultrasonographer
- Scans reported independently by 3 different individuals
- Scans graded – ‘normal’, ‘definite steatosis’ and ‘probable steatosis’
- Scans repeated by the same ultrasonographer after 3 year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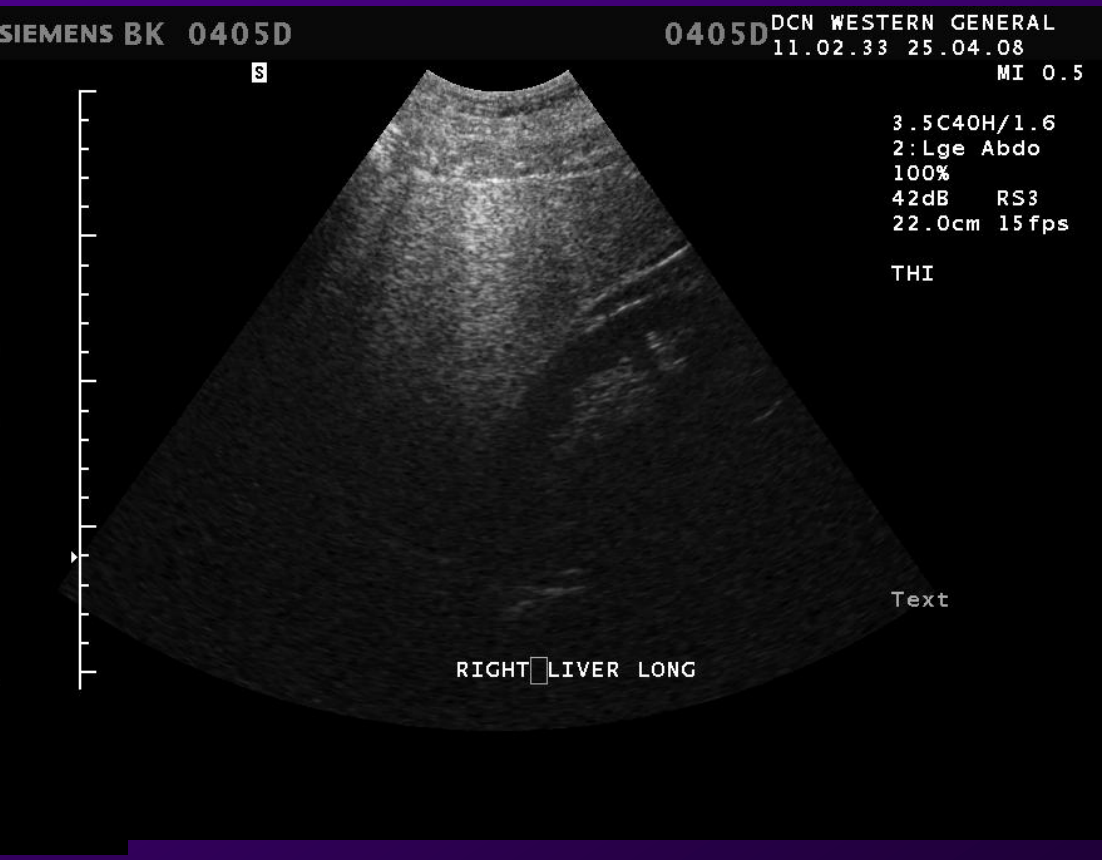
RIGHT LIVER LONG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100%
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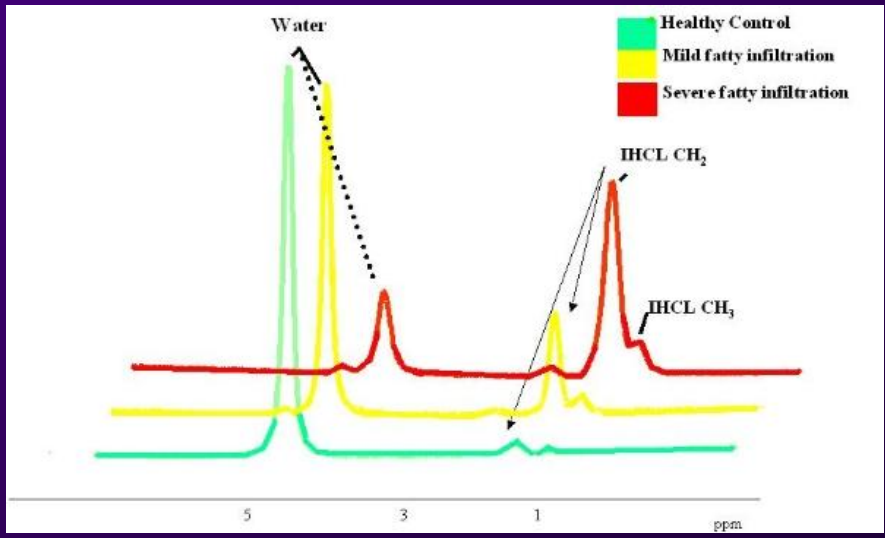
THI
Text
RIGHT LIVER LONG

MRI Sub-study

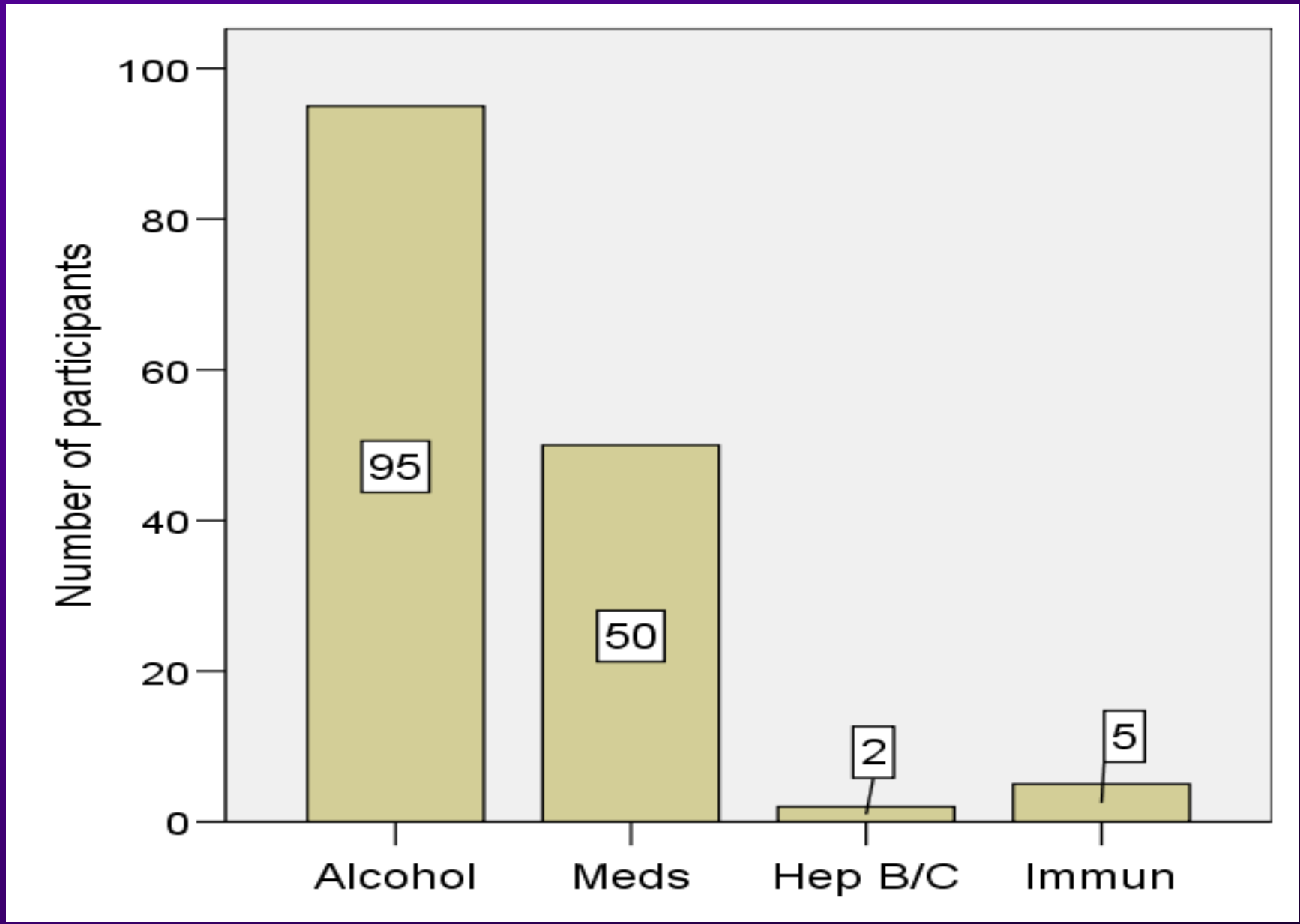
- 60 subjects underwent proton MR spectroscopy of the liver
- Median Hepatic Fat Fraction (IQR):
- ‘Normal’ 4.1 (1.2-5.7) %
- ‘Probable steatosis’ 4.1 (3.1-8.5) %
- ‘Definite steatosis’ 19.4 (12.9-27.5) %



Williamson et al Clin Radiol 2011; 66: 434-439

How do we Define NAFLD?

- Liver disease in the absence of a secondary cause
  - Alcohol
  - Viral
  - Autoimmune
  - Drugs - amiodarone, tamoxifen, glucocorticoids
  - Haemochromatosis
  - Alpha-1 anti-trypsin deficiency


Number of participants
100
80
60
40
20
0
95
50
2
5
Alcohol
Meds
Hep B/C
Immun

Steatosis Prevalence and Associated Factors

- 56.9% had steatosis
- 42.6% had NAFLD
- Associated factors
  - BMI
  - Shorter duration of diabetes
  - HbA1c
  - Use of metformin

Williamson et al Diabetes Care 2011; 34: 1139-1144

Relationship of Markers of Liver Disease with Conventional LFTs

	Normal	Steatosis
Bili (umol/l)	8.6 ± 4.6	8.0 ± 3.5
Bili > 18 (no. (%))	9 (4.6)	5 (1.7)
ALT (U/l)	30.1 ± 9.8	35.5 ± 13.7
ALT > 50 (no. (%))	5 (2.5)	29 (9.9)
log GGT	1.1 ± 0.3	1.3 ± 0.3
GGT > 55 (no. (%))	11 (5.6)	24 (8.2)

Change in Steatosis Over 3 years

- 56.9% had steatosis at baseline
- 50.5% had steatosis at 3 years
  - 16% had steatosis that regressed (2% had falling platelet count)
  - 8% developed ‘new’ steatosis

Liver Function Tests

- 16% had at least one abnormal LFT at baseline
  - Remained abnormal over 4 years in 57.5%
  - Improvement associated with male sex and lower BMI.
- 8.1% of people with normal LFT's at baseline developed at least one abnormal LFT over 4 years
  - Progression associated with younger age

‘Hard’ Liver Outcomes

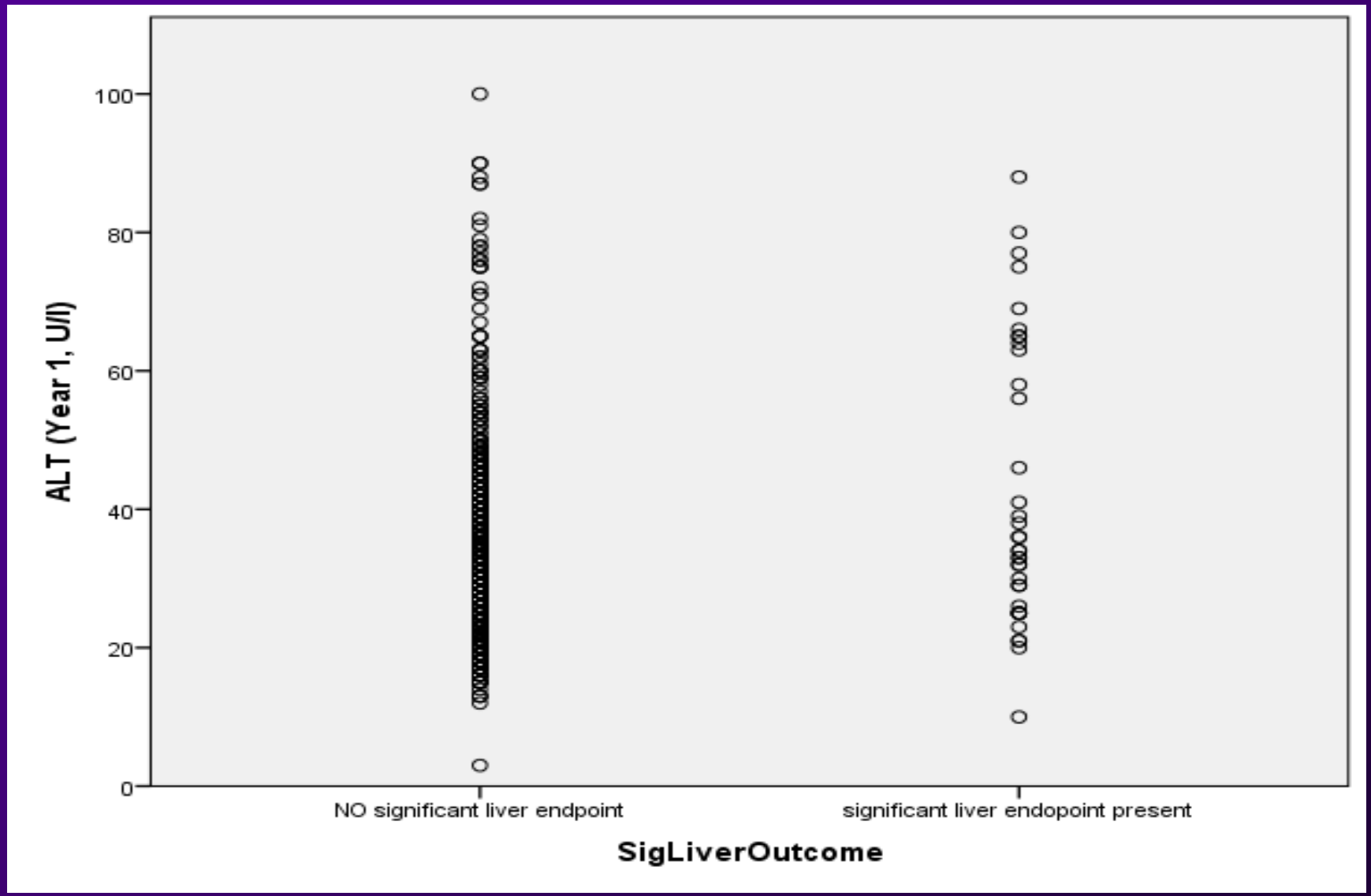
- Hepatocellular carcinoma
- Varices
- Other features of portal hypertension

- Questionnaire given to patients at time of second USS
- Record linkage by ISD
- Screening of electronic patient records

‘Hard’ Liver Outcomes

- 124 patients were referred after the initial study visit – most not seen or discharged after 1 visit
- After 5 years of follow-up, 37 patients (4%) had a ‘hard’ liver outcome:
  - 8 Hepatocellular carcinoma
  - 10 Varices
  - 19 Cirrhosis or other features of portal hypertension
- 2 HCC and 8 cirrhosis cases had been identified at the time of the original scans…so true incidence was 2.9%
- 20 patients developing liver outcomes were not identified as being at ‘high risk’ after the initial screening

	Liver Outcome	No Liver Outcome	p-value
Steatosis %	64.0	56.6	>0.05
Secondary cause %	44.0	20.2	0.010
Spleen > 13 cm	36.0	3.9	<0.001
Platelets <150	33.3	3.1	<0.001
ALT U/l	42.2 (18.2)	33.2 (12.6)	0.021
ALT >50 u/l %	32.0	12.8	0.001
BMI kg/m-2	33.8 (6.0)	31.3 (5.7)	0.027
WC cm	112.2 (12.9)	106.6 (12.8)	0.032


ALT (Year 1, U/l)
100
80
60
40
20
0
NO significant liver endpoint
significant liver endopoint present
SigLiverOutcome

Prevalence, Incidence, and Prognosis of Hepatobiliary Disease in Community-Based Patients with Type 2 Diabetes: The Fremantle Diabetes Study

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Context: Few studies have examined morbidity and mortality associated with hepatobiliary disease in diabetes. Most have used administrative databases and/or have had limited/incomplete data including recognized risk factors for hepatobiliary disease.

Objective: The objective of the study was to explore the relationship between type 2 diabetes and hepatobiliary disease in well-characterized patients with detailed risk factor data including viral hepatitis status and hemochromatosis genotype.

Design: This was a community-based longitudinal observational study.

Setting: The study was conducted in an urban Australian community.

Patients: The study included 1294 patients of mean ± SD aged 64.1 ± 11.3 yr and 5156 age-, gender-, and ZIP code-matched nondiabetic controls.

Main Outcome Measures: Prevalent and incident hepatobiliary disease and hepatobiliary disease-related deathwere measured. Competing risks proportional hazard models provided independent associates of these end points.

Results: During 13,705 patient-years (mean 11.5 yr), 144 patients had an initial hepatobiliary disease-related hospitalization/cancer registration *vs.* 403 controls during 63,937 person-years of follow-up, an incidence rate ratio of 1.66 (95% confidence interval 1.37–2.02). Incident hepatobiliary disease was associated with a lower glycosylated hemoglobin and higher urinary albumin to creatinine ratio. Nearly half of the patients (49.9%) died during follow-up [crude mortality ratio *vs.* nondiabetic controls 1.97 (1.16–3.32)], and 21 (3.3%) from hepatobiliary disease including two cases of cirrhosis attributable to nonalcoholic steatohepatitis. Hepatobiliary disease-related death was independently predicted by prior hepatobiliary disease, hepatitis C seropositivity, retinopathy, and peripheral neuropathy; higher educational level and higher fasting serum glucose were protective.

Conclusions: Hepatobiliary disease and associated mortality are increased in type 2 diabetes. Multiple factors including fatty infiltration, microangiopathy, and direct glucotoxicity are likely to contribute, but hospitalization and death due to cirrhosis from nonalcoholic steatohepatitis appear uncommon. (***J Clin Endocrinol Metab* 97: 1581–1588, 2012**)

There are relatively few studies that have examined morbidity and mortality associated with hepatobiliary disease in patients with type 2 diabetes. A recent Canadian study involving an administrative database found that newly diagnosed diabetes was associated with a 77% increased risk of subsequent liver cirrhosis, liver failure, or liver transplantation (1). In an Italian community-based study, the standardized mortality ratio

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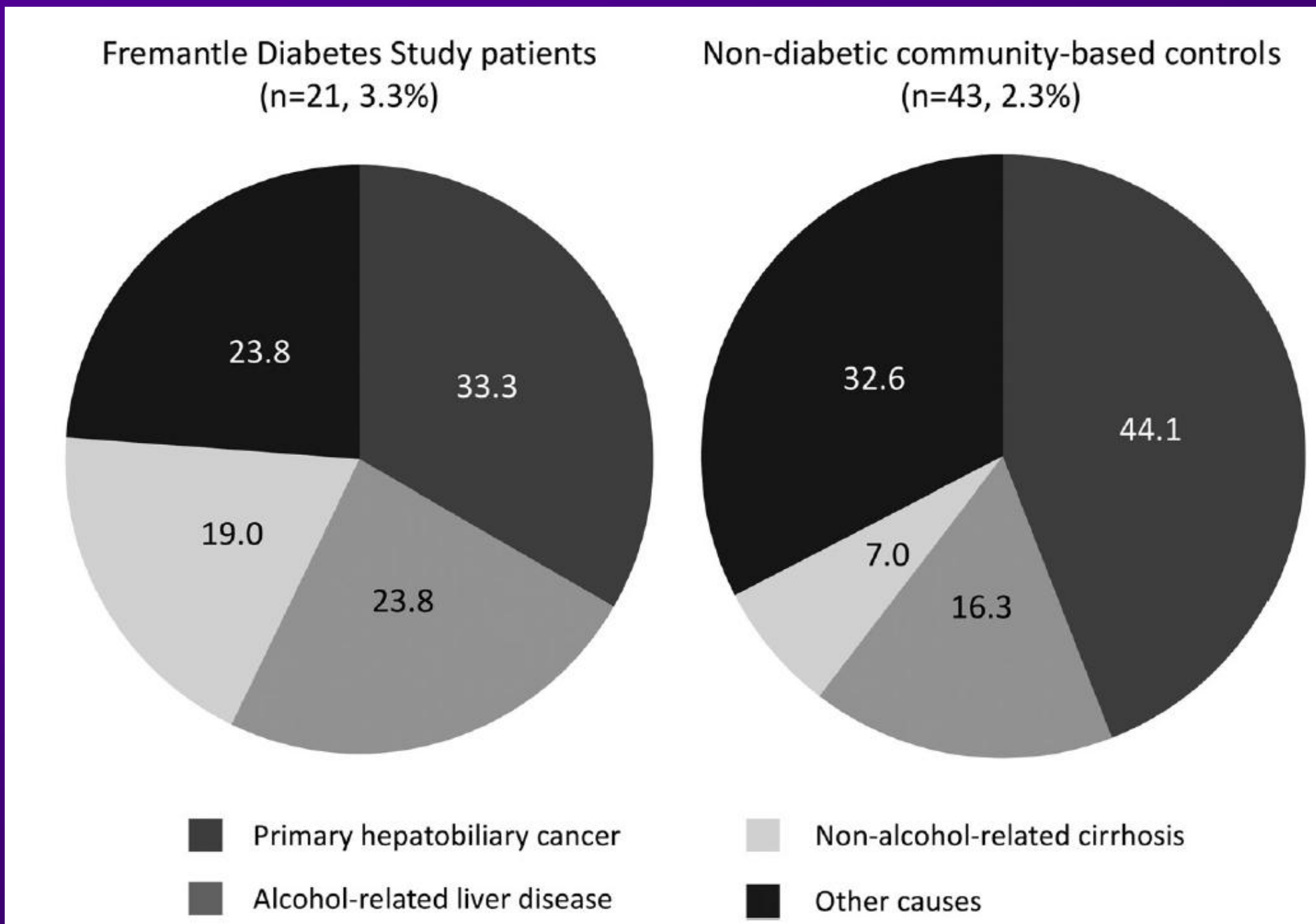
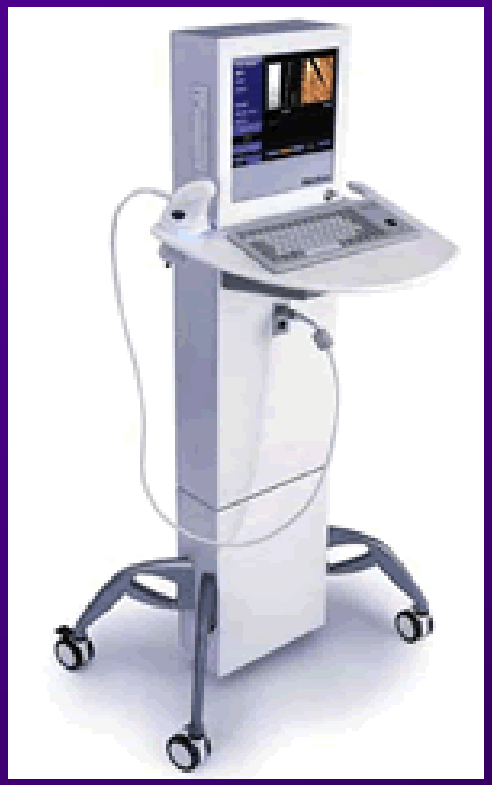
Abbreviations: CI, Confidence interval; FDS, Fremantle Diabetes Study; HbA_{1c}, glycosylated hemoglobin; *HFE*, hemochromatosis gene; ICD, International Classification of Disease; IRR, incident rate ratio; NAFLD, nonalcoholic fatty liver disease; WA, Western Australia.


Fremantle Diabetes Study patients
(n=21, 3.3%)
23.8
33.3
19.0
23.8
Non-diabetic community-based controls
(n=43, 2.3%)
32.6
44.1
7.0
16.3
Primary hepatobiliary cancer
Non-alcohol-related cirrhosis
Alcohol-related liver disease
Other causes



Why Refer to a Hepatologist?

- To get a diagnosis
  - Is there significant fibrosis?
- To assess for complications
  - Varices
  - HCC surveillance
- To get treatment

Who to Investigate

- ???? Very overweight people
- Persistent abnormal LFTs
  - USS (including spleen size)
  - Ferritin/transferrin saturation
  - Hep B and C serology
  - Autoimmune profile
  - Platelet count
  - ?AFP

Who to Refer to a Hepatologist

- Persistent abnormal LFTs – ALT more than twice the upper limit of normal
- Low platelets
- Enlarged spleen
- Evidence of a secondary cause

Summary

- Type 2 diabetes is strongly associated with NAFLD
- NAFLD is a non-diagnosis, that has no clear definition
- Steatosis is very common, but might not be a good indicator of likelihood of progression
- 2.9% of people with Type 2 diabetes developed a significant liver complication over 5 years
- We need better tools to identify liver fibrosis
- ‘Normal LFTs’ DO NOT MEAN ‘normal liver’

Edinburgh Type 2 Diabetes Study

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