Big questions in diabetes well, a glaswegian view

Naveed Sattar
BHF Cardiovascular Research Centre
University of Glasgow

What works and what may not work for CVD prevention

What works?

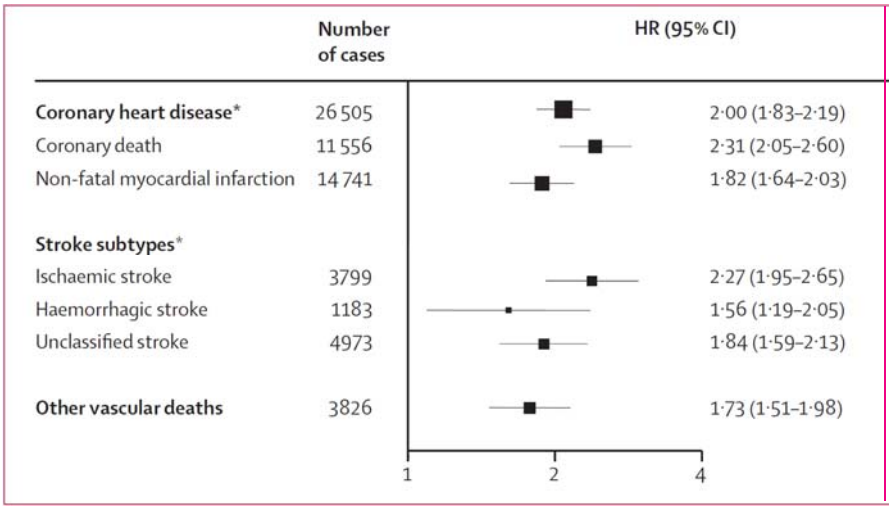
- **Statins**
- **BP reduction**
- **Smoking cessation**
- ***Glucose lowering?***
  - *Modality? Why did EMPAREG work so well?*
  - *Metformin best? Need trial*

What remains uncertain

- ***Lifestyle intervention?***
- **Fibrates?**
- **Aspirin – primary prevention? No**

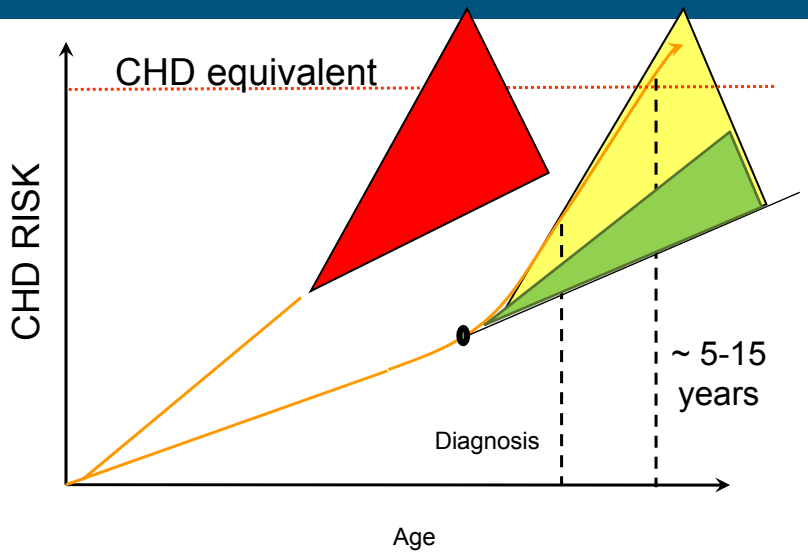
ON average diabetes doubles CVD risk

ERFC (2010) Lancet



Hazard ratios for vascular outcomes DM vs. no DM

Diabetes and CVD risk: duration Diagnosis and age of onset matter

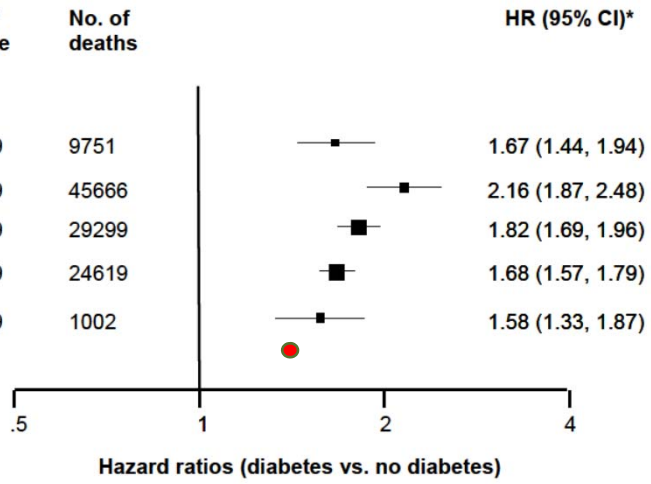


Sattar (2013) Diabetologia (several studies support concept)

CVD RISKS HAVE LESSEND OVER YEARS

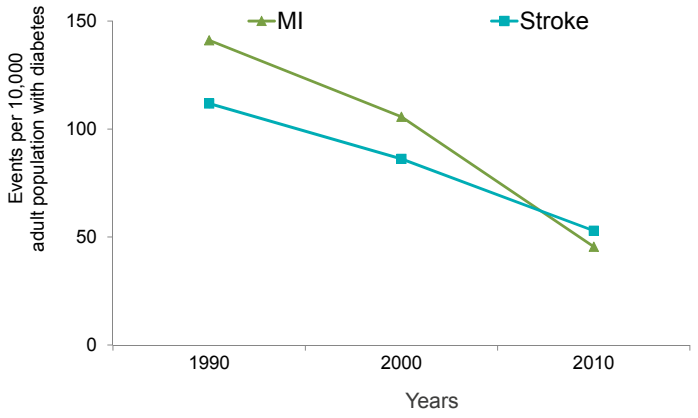
PS – not showing Swedish data – as you know these well and excellent

Mortality in DM declined last 3 decades



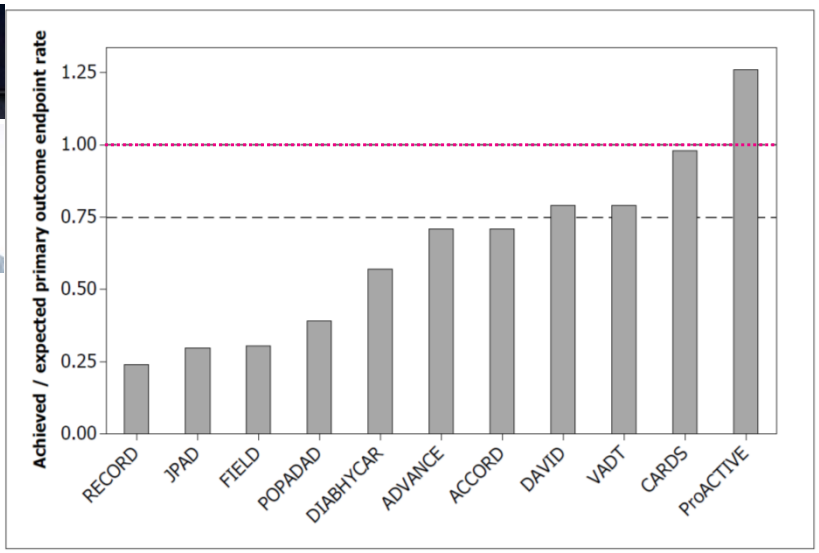
ERFC (2011) NEJM

Diabetes-related CV complications have declined with improved care, but substantial burden remains



CV, cardiovascular; MI, myocardial infarction.
Adapted from Gregg EW, et al. *N Engl J Med.* 2014;370:1514–1523.

Prior DM Trials mostly underpowered
Preiss, Sattar, McMurray (2011) AHJ 2010



T2DM – doubles CVD risk and other risks too

- **CVD risk double <u>on average (but heterogeneous)</u>**
  - Decade of diabetes…..towards CHD risk equiv.
  - Or proteinuria / low eGFR
- **CHF, PAD commonest 1ST CVD events in DM**
  - Shah et al (2015) Lancet DE
- **Statins lower HF risks**
  - Preiss et al (2015) EHJ

Summary: doing well in high income countries

- **Clear evidence ⇓ CVD in DM over several decades**
  - Better management CVD risk factors big part
    - BP and LDL-c reduction >> glucose reduction
    - But many remain sub-optimally treated
- **Greater survival and longer glycaemia exposure so more renal outcomes – competing risks?**
  - Review: Gregg, Sattar, Ali TLDE submitted on trends over time – mostly US but key data EU, other

Key points which you know

- **In DM alone**
  - MI, stroke hyperglycaemia deaths, amputations down
  - ESRD down but by ½ above
  - Per unit total population, ESRD actually up by 90%
- **Biggest CVD reductions in older folk**
  - But trends by SES, ethnicity, younger age groups?
- **Future:**
  - set for more cognitive /physical disability /more renal / more specific cancers?

Questions?

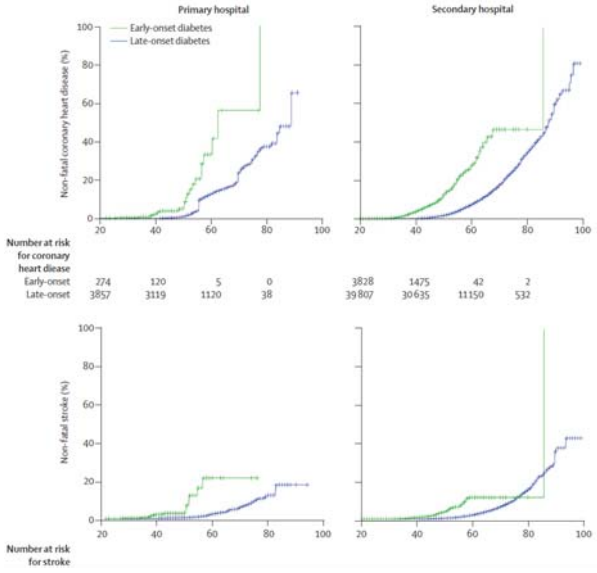
- **Young type 2 and risk?**
- **Ethnicity and risk? Ongoing in few places**
- **CVD-related questions?**
  - Heart failure / PVD / A fib / DM plus CVD risks
- **Liver-related questions? Overblown?**
- **Cognitive decline?**
- **Smokers and BMI at diagnosis?**
- **Gender and risk?**
- **Change in risk factors over time?**

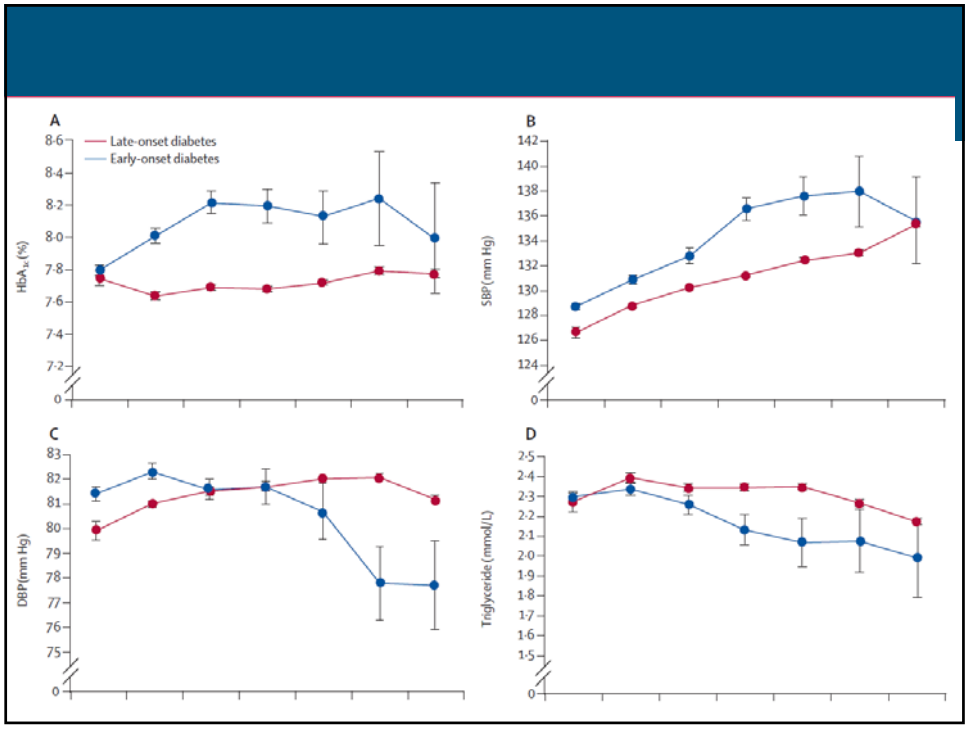
Younger T2DM and risk

- **Why are younger folk at much higher risk?**
  - Extend recent Chinese data
  - Trajectories of risk factors over time? More obese
  - Simply duration? HR massively attenuated by duration (co-linear to risk factor status?)
  - Less aggressive risk factor management?

Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study

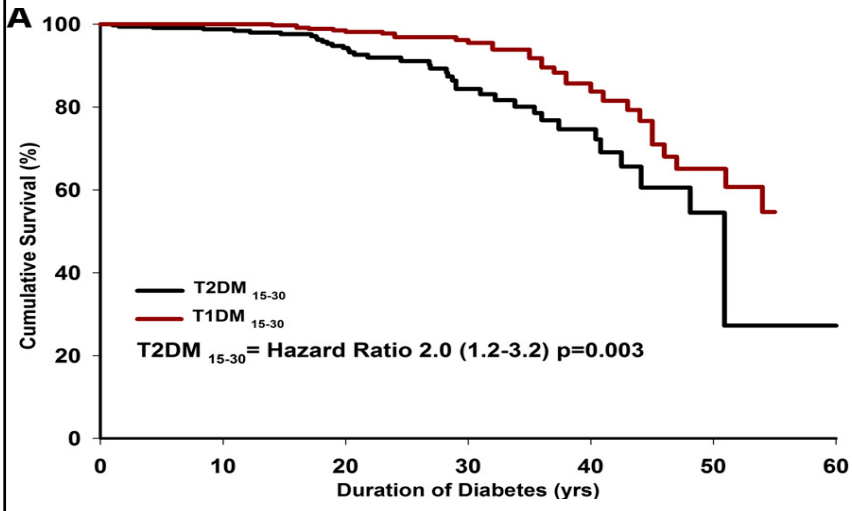
Xiaoxu Huo*, Lefei Gao*, Lixin Guo*, Wen Xu, Wenbo Wang, Xinyue Zhi, Ling Li, Yanfeng Ren, Xiuying Qi, Zhong Sun, Weidong Li, Qiuhe Ji, Xingwu Ran, Benli Su, Chunming Hao, Juming Lu, Xiaohui Guo, Hanjing Zhuo, Danyi Zhang, Changyu Pan, Jianping Weng, Dayi Hu, Xilin Yang, Linong Ji





Long-Term Complications and Mortality in Young-Onset Diabetes

Type 2 diabetes is more hazardous and lethal than type 1 diabetes



Constantino et al (2013) Diabetes Care ePub

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- **CVD-related questions?**
  - Heart failure / PVD / A fib / DM plus CVD risks / DRUG effects
- **Liver-related questions? Overblown?**
- **Cognitive decline?**
- **Smokers and BMI at diagnosis?**
- **Gender and risk?**
- **Change in risk factors over time?**

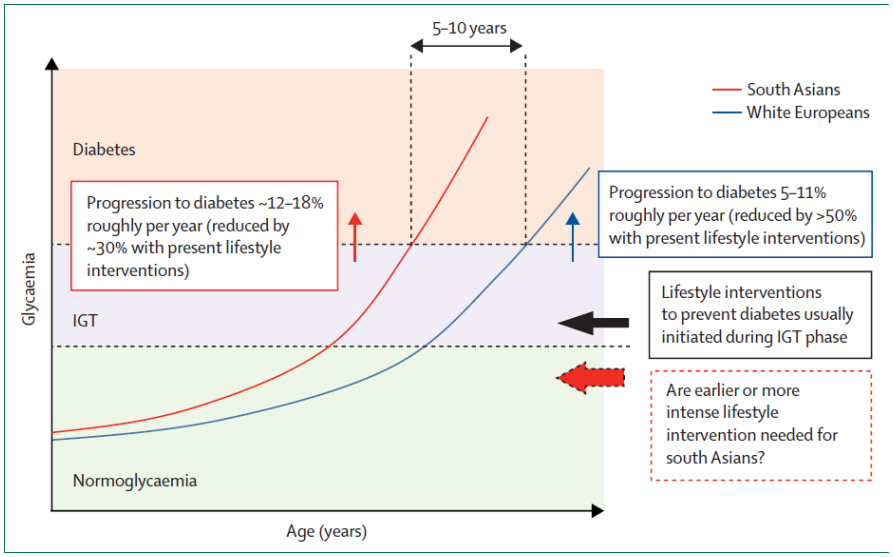
Ethnic risks with diabetes in high income countries - suprising

- **What are risk by ethnic groups?**
  - Some evidence South Asians with diabetes lower mortality – why? Risk factors levels by ethnicity
  - Earlier exposure to statins (better response to statins?) and BP medications?
  - Lower smoking rates?
  - So less CVD death but same amount or more of microvascular disease
- **Do South Asians have worse trajectory of glycaemia over time – other ethnicities?**

Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management

*Naveed Sattar, *Jason M R Gill

South Asians, particularly when living in high-income countries, are at a substantially elevated risk of type 2 diabetes Lancet Diabetes Endocrinol 2015



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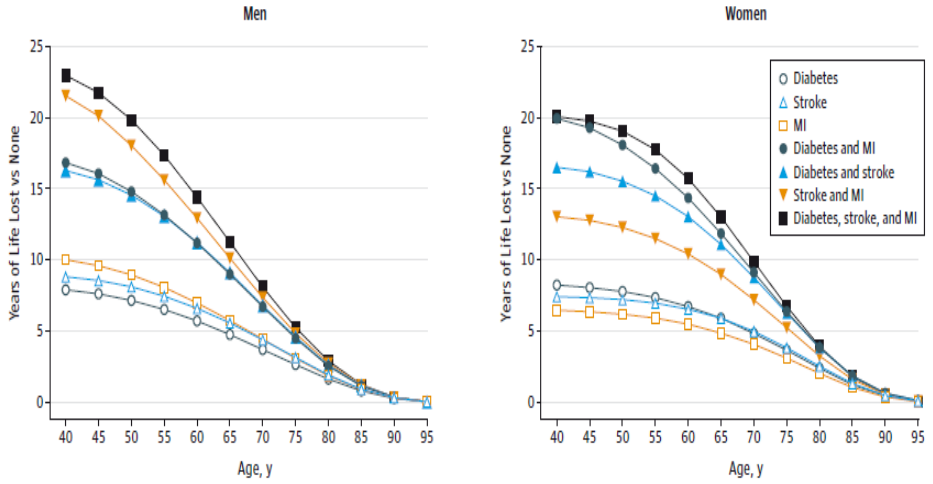
CVD – BIG questions

- **Why risks lower? Risk factor management?**
  - Change in risk factors over time, BP, lipids YES
  - Earlier diagnosis? HbA1c at diagnosis lower? YES?
  - Slower rise in HbA1c over time? UNSURE
- **How are the patterns of CVD changing?**
  - Less fatal events?
  - More incident HF / PVD? UK data
  - What makes diabetes a CVD risk equivalent?

CVD – guideline issues

- **Risk score for CVD – do we need it? (with Scots?)**
  - DM getting statin 'ahead' of non-DM
  - 10 year risk versus lifetime risk model
  - Fire and forget; all >40 statins
  - Who < 40 should be on statin
- **How is survival OR HF risks in patients with**
  - DM + CVD
  - DM + CKD /proteinuria
  - Vs CVD alone or CKD alone

Background: Estimated Future Years of Life Lost Due to Diabetes with and without MI or stroke



ERFC et al. *JAMA* 2015;314:52–60.

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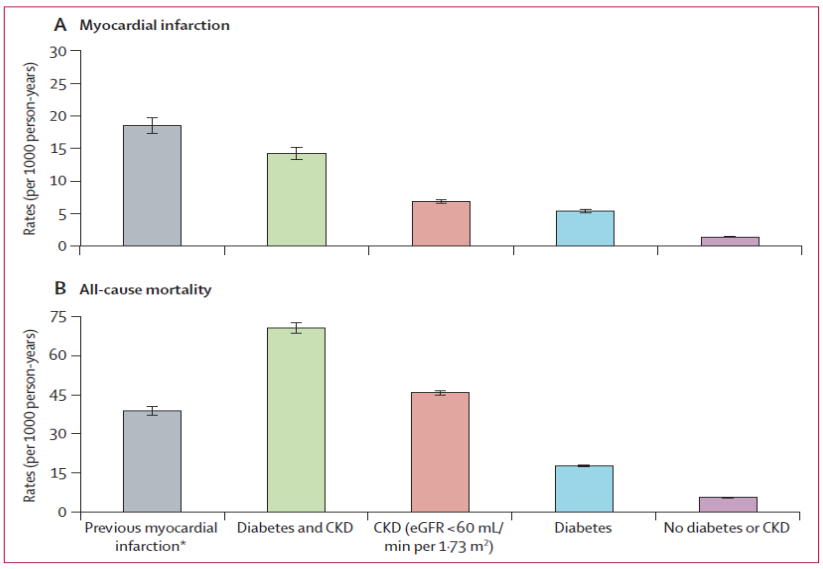
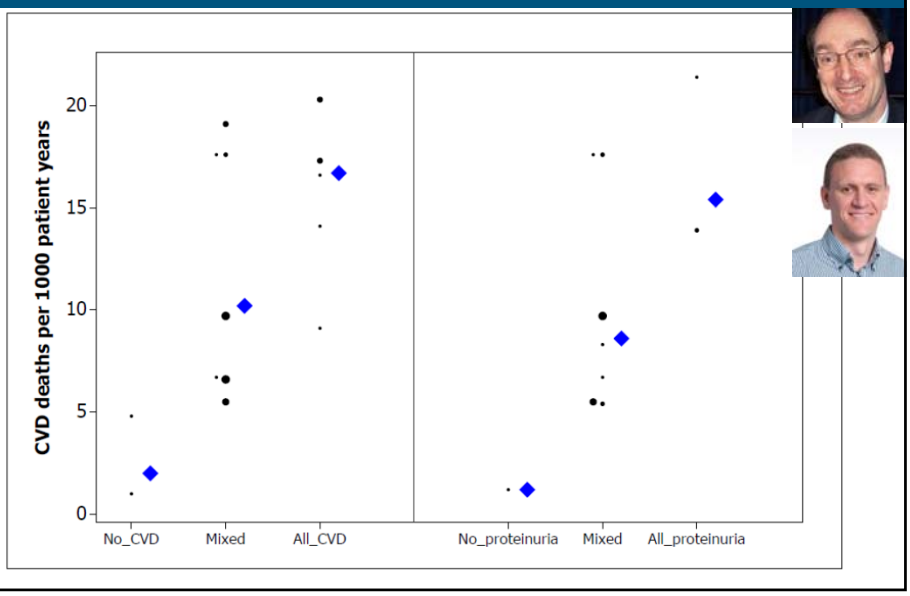
Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study

Marcello Tonelli, Paul Muntner, Anita Lloyd, Braden J Manns, Scott Klarenbach, Neesh Pannu, Matthew T James, Brenda R Hemmelgarn, for the Alberta Kidney Disease Network



29 RCTs DM patients: simple predictors of risk Preiss, Sattar, McMurray (AHJ 2010)



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thebmj

BMJ 2014;349:g4596 doi: 10.1136/bmj.g4596 (Published 29 July 2014)

CLINICAL REVIEW

Non-alcoholic fatty liver disease

Naveed Sattar *professor*[1], Ewan Forrest *consultant*[2], David Preiss *clinical senior lecturer*[1]

[1]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, UK; [2]Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, UK

Typical pattern in suspected NAFLD

- **Mrs B referred for abd U/S: discomfort:**
- **Age 56, BMI 28 kg/m^2, no alcohol**
- **Family history T2DM**
- **ALT 48 U/L, AST 32 U/L**
- **Chol 5.2, trig 4.1, HDL-c 1.0 mmol/L**
- **Glycaemia tests: FBG 6.2mmol/l, HbA1c 43mmol/mol**
- ***US: ⇑hepatic echogenicity***

What are the risks of liver disease in diabetes – should we worry?

- **Scottish data in press J Hepatol**
  - Vs non-DM
  - Variation by SES and sex –
- **Unable to ascertain NASH – NAFLD not systematically screened for**
- **Clinically which DM patients at highest risk of NASH and sequalae**

Type of liver disease	Men		Women	
	Age-adjusted	Age and SES quintile adjusted	Age-adjusted	Age and SES quintile adjusted
Alcoholic liver disease*	1.51 (0.82- 1.80)	1.38 (1.15- 1.65)	1.77 (0.99- 3.20)	1.57 (1.28- 1.93)
Autoimmune liver disease	1.50 (1.12- 2.01)	1.50 (1.12- 2.01)	1.27 (1.04- 1.55)	1.25 (1.04- 1.49)
Hemochromatosis	1.70 (1.41- 2.05)	1.67 (1.43- 1.94)	1.67 (1.25- 2.23)	1.60 1.23- 1.97)
Hepatocellular carcinoma	3.44 (2.85- 4.17)	3.36 (2.97- 3.81)	3.69 (2.99- 4.56)	3.55 (3.02- 4.17)
Non-alcoholic fatty liver disease*	3.15 (2.50- 3.97)	3.03 (2.68- 3.43)	5.36 (4.41- 6.51)	5.11 (4.45- 5.87)
Viral liver disease	1.47 (0.54- 3.98)	1.28 (0.86- 1.92)	2.54 (1.18-5.47)	2.20 (1.52- 3.18)

* See table 2 for rate ratios stratified by SIMD quintile

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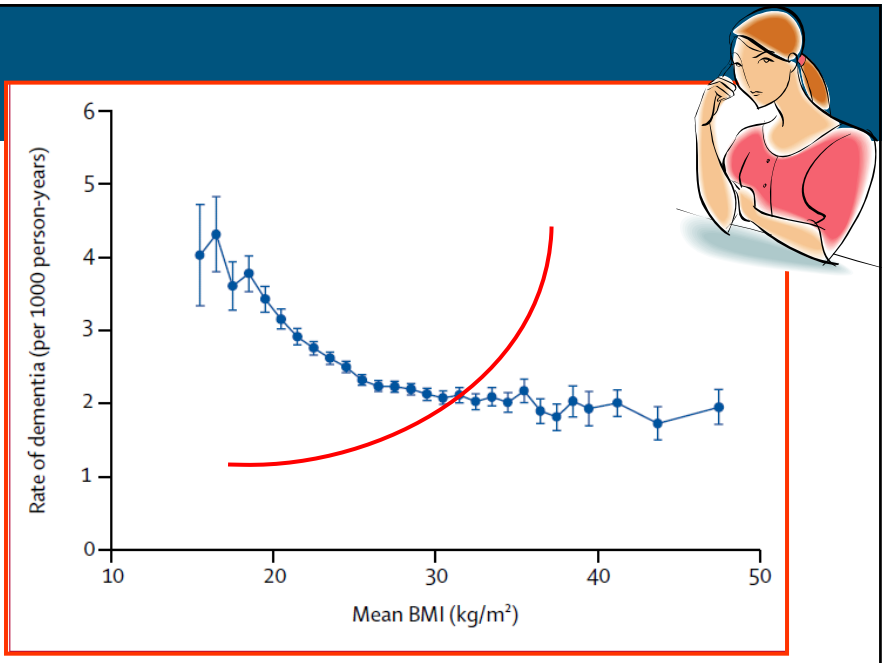
- **Cognitive decline? If more CVD, HBP etc, then dementia up, right? complex**
- Smokers and BMI at diagnosis?
- Gender and risk?
- Change in risk factors over time?

Obesity and dementia – now prepared to be confused

- **Surely higher BMI linked to dementia risk**
- **BMI – CVD, DM, HBP etc**
- **All outcomes give greater cognitive decline**
- **BUT recent report says reverse**
  - Qizilbash et al Lancet DE 2015
  - Higher BMI linked to lower dementia risk
  - Unintentional weight loss (slow) many years before dementia so lower DM development



Qizilbash et al Lancet DE 2015

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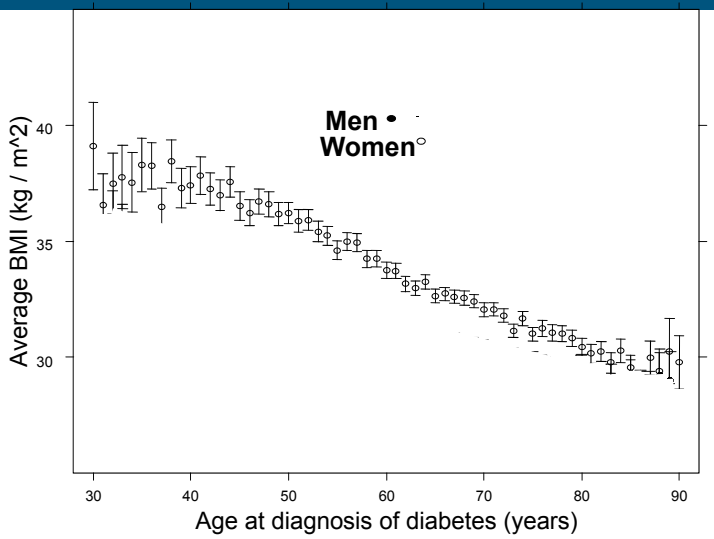
Men get diabetes at lower BMI across lifecourse
what about smokers / different ethnicities

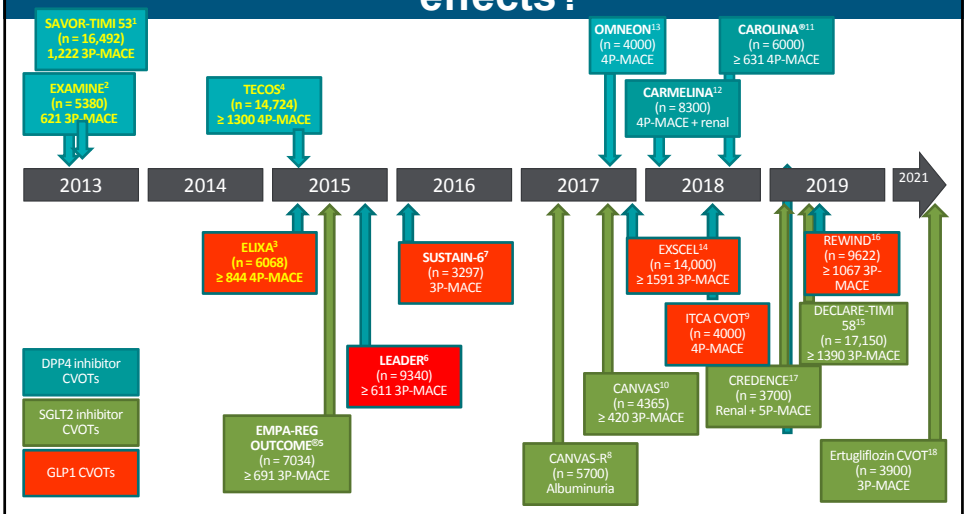


Logue et al (2011) Diabetologia

BMI and mortality risk in DM

- **U-shaped?**
- **Repeat with robust protocol to lessen reverse causality**
  - Remove DM + comorbidity linked to weight loss
  - Examine weight trajectories at lower BMI
  - Remove first 5 years
- **Also HbA1c vs outcomes**
  - Lower HbA1c enriched for (intentional) weight losers?

CV trials: 5 down, many to come
can epidemiology match trials on drug effects?



Timings estimated from ClinicalTrials.gov.

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Thanks

- Scots colleagues: S Wild, H Colhoun, et al
- ERFC – led by John Danesh et al
- Martin Rutter et al – CPRD work
- Ed Gregg and Mo Ali USA