Norfolk Diabetes
NDPS
Prevention Study

Norfolk Diabetes Prevention study (NDPS) and the NDPP

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“ There are entirely too many diabetic patients in the country. Statistics for the last thirty years show so great an increase in the number that ……. the outlook for the future would be startling. ”

“ The physician should take pride in the prevention of diabetes in his practice. Obese patients should be frankly told that they are candidates for diabetes ”

Joslin EP.
The Prevention of Diabetes Mellitus

JAMA 1921; 76 (2):79-84.

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- **Evidence for Type 2 diabetes prevention in the real world.**
- **What are the gaps in current understanding.**
- **NIHR Norfolk Diabetes Prevention Study (NDPS).**

  BMC Public Health 2017 17: 37
  www.norfolkdiabetespreventionstudy.nhs.uk

- **Capacity planning, risk stratification, and implementation for NHS England DPP**

What does 'at high risk of diabetes' mean for people with non - diabetic hyperglycaemia (NDH) ?

- **Meta - analysis of 70 studies examining transition rates to Type 2 diabetes in populations with IFG or HbA1c 6 – 6.4 mmol/mol suggest an annualised incidence of only 3.5 – 4.7%.**
- **Transition rates may approach only 1 – 1.5% annually in subgroups with HbA1c 42 - < 48 mmol/mol and normal fasting glucose.**
- **Substantially less than modelling based on other glycaemic categories and original prevention trials**

Morris DH, Khunti K, Achana F et al. (2013) Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia 56: 1489– 1493.

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Baseline characteristics of all USA trials (n = 40) versus DPP (Mudaliar et al 2016 PLOS Med)

	DPP trial	Composite trials (mean; IQR)	
Age (yrs)	50.6	50.8 (49.0 – 56.4)	
BMI (kg/m2)	33.7	34.8 (32.2 – 36.6)	
Weight (kg)	93.5	99.3 (91.5 – 101.7)	
HbA1c (%)	5.8	5.9 (5.7 – 6.0)	
Fasting glucose (mg/dl)	106.3	104.6 (99.0 – 107.6)	
Screening	IGT/IFG	IFG/IGT/Risk score	
Individual sessions	100%		16.7 %
Follow up	2.8 years		9.3 months
Maintenance sessions	100%		62.5%
Personnel	Dietitians Coaches with masters in exercise physiology or behavioural psychology		Mixed backgrounds Internet based Lay volunteers

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Comparison of outcomes from DPP versus Community Trials

Mudaliar et al 2016 PLOS Med

	Studies	Baseline mean	Mean change (95% CI)	DPP Trial
Weight (kg)	48	99.3	- 3.77 (-4.5, -2.99)	- 5.6
Glucose (mg/dl)	21	104.6	- 2.40 (- 3.59, - 1.21) **	- 5.0

** Fasting plasma glucose change not significant for intervention groups selected using risk calculators rather than antecedent glucose data.

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Meta analysis of 49 diabetes prevention trials by 2017 (Barry et al. BMJ 2017)

- 19 used the development of diabetes as a primary outcome measure.
  - Some trials began with this outcome but during substituted it for weight reduction or glycemic markers because of low recruitment.
- 20 showed a clinically significant reduction in weight between the groups
- 15 showed a clinically significant improvement in glycemic markers
- 23 showed some difference in favour of the intervention arm in the number of people developing diabetes, but this difference <u>was significant only in seven of those trials</u>

Meta analysis of 49 diabetes prevention trials by 2017 (Barry et al. BMJ 2017)

- Lifestyle interventions reduced the relative risk of developing diabetes by 31% (95% confidence interval 15% to 44%) if the intervention lasted six months to 24 months.

- This translates to 69 (95% confidence interval 56 to 85) out of 1000 people in the lifestyle intervention group developing diabetes compared with 100 out of 1000 without the intervention, and a number needed to treat (NNT) of 33 (95% confidence interval 23 to 67).

- NNT of 33,000 for 1,000 prevented cases T2DM in 9 – 24 months intervention

- Identify and intervene models (based on trial culture) and wider population based prevention strategies.

Prevalence of pre-diabetes by diagnostic test with WHO criteria, showing overlap with all three tests. *Eleanor Barry et al. BMJ 2017;356:bmj.i6538*

a = 4.7% isolated IFG

b = 24.4% isolated IGT

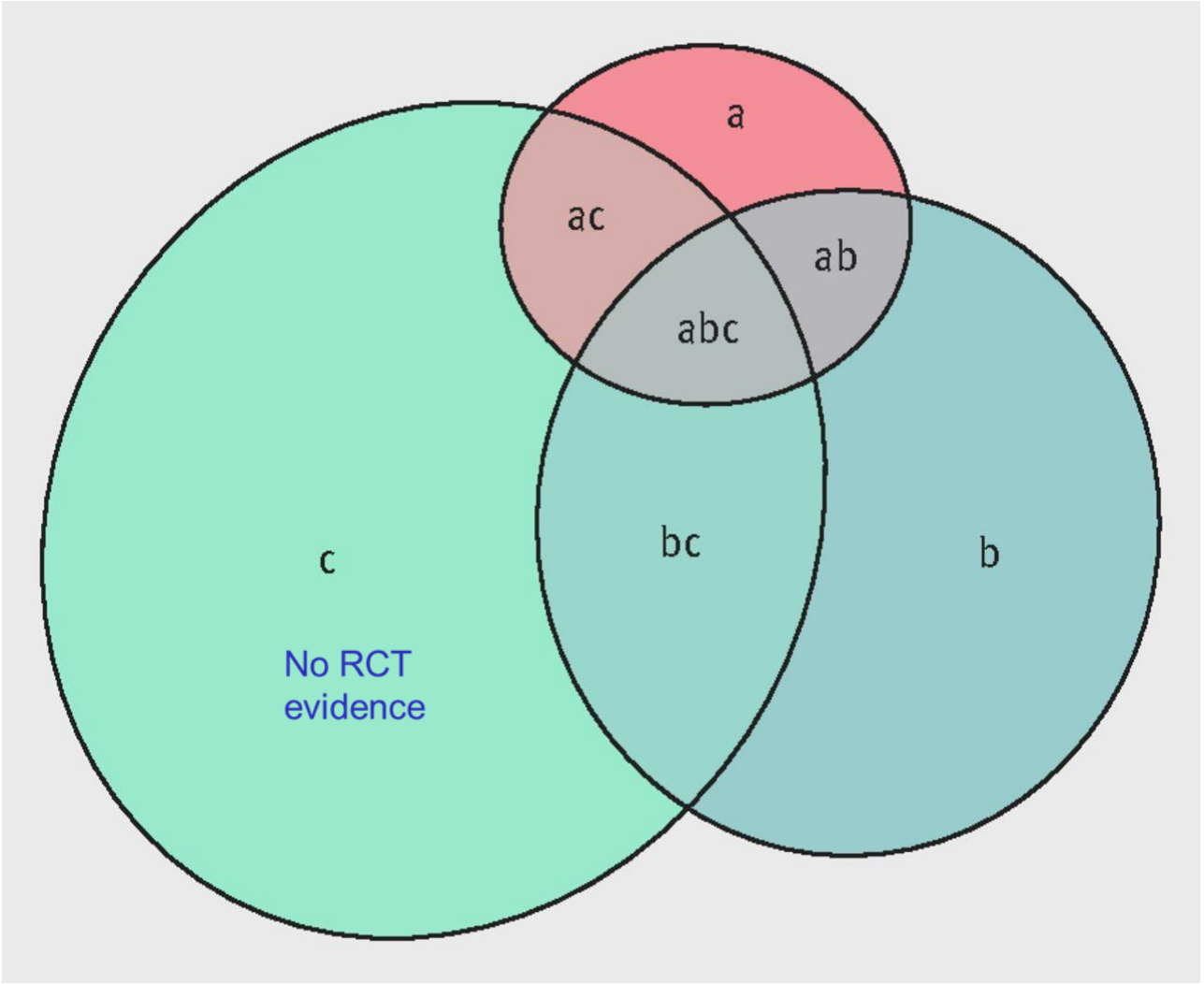
c = 47.8% isolated HbA_{1c}

ab= 2.9% IFG+IGT

ac= 4.1% IFG+HbA_{1c}

bc =12.2% IGT+HBA_{1c}

abc =3.9% IGT+IFG+HbA_{1c}



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72% (normal result)

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- ✓ Early large scale RCTs showed benefit in highly supportive research environment.
- ✓ Recognised very early that this model was unaffordable in terms of resource and time in most health care systems, and the need for more pragmatic interventions, delivered in groups, and based in real word settings.
- ✓ Translation to other modes and sites of delivery has been less impressive, in terms out outcomes, with NNT of 33 for < 2 years intervention, limited RCT evidence in many populations, and fading of benefit after trial.
- ✓ Risk of progression to T2DM is more modest in current 'high risk' groups than often assumed.
- ✓ Risk of progression amplified using multiple glycaemic categories to assess risk
- ✓ The primary modern 'at risk' groups with NDH /IFG have little trial evidence for outcomes (isolated NDH HbA1c 42 - < 48 mmol/mol)
- ✓ Screen and treat approach (trial culture), or population approach, or mixed approach in line with WHO ?

Radically upgrading diabetes prevention in England

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Lancet Diabetes and Endocrinology March 15th 2015 online

*Mahiben Maruthappu, Harpreet Sood, Bruce Keogh

- National diabetes prevention programme (DPP) launched in 7 large CCG demonstrator sites in population of 1.8 million….
- The programme will initially target up to 10,000 people at high risk of T2DM diabetes ….
- Test innovative ways of finding those at risk ie using the NHS Health checks …
- Combination of physical activity and diet focused behavioural modification..
- Peer support with telephone and online assistance …..
- National framework contract for a diabetes prevention service ….
- Broadly similar to NIHR diabetes prevention programme UEA – IFG (2008) and NDPS (2011 -) proposals and delivery

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- Based CRTU at UEA Norwich since 2008
- 8 satellite screening and intervention sites
- £ 3.225 M NIHR programme grants
- Substantial CRN support
- Population covered 1,587,900
- 144,000 at risk people in 135 GP practices
- 13,682 screened and 15,437 registered
- 1,762 on trials ,reporting in 2018

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Timelines for NDPS

- The Norfolk Diabetes Prevention Study (NDPS; £2.629M ; 5 years; NIHR) was given final ethical approval on 13th January 2011

- The NDPS follows an antecedent 2 year NIHR programme grant (2007 – 2009; UEA – IFG; £ 800 k) where all elements of the programme were tested and developed

- The intervention comprises 6 core seminars (months 1-3) and 15 maintenance after-core facilitated discussions over 3.25 years months delivered by a Diabetes Prevention Facilitator (DPF) and a diabetes prevention mentor (DPM) in groups, with Type 2 diabetes acting as a lay trainer.

Quality markers and unique elements in NDPS

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- **Multiple ‘real world’ NHS glycaemic ‘prediabetes’ categories (not IGT)**
- **Limited impact on general practice**
- **Concurrent randomisation of screen detected Type 2 diabetes.**
- **Group delivery of intervention**
- **Intervention delivered by lay trainers with Type 2 diabetes**
- **Exercise data**
- **Strong core behavioural science team**
- **Process analysis**

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Original programme structure

Project 1: A high volume (n = 10,000) primary care based screening programme in participants at higher risk of T2DM, based on age and body mass index (BMI)

Project 2: Main trial (n = 1,026) of our diabetes intervention (standard intervention, or standard intervention plus lay diabetes prevention mentors) in target glycaemic risk categories compared to controls

Project 3: Recruitment of diabetes prevention mentors (DPM)

Project 4: Main trial of our diabetes intervention (standard intervention, or standard intervention plus DPM) in screen detected T2DM compared to controls

Project 6 Trial evaluating the HbA1c intervention effect size in subset with (42 – 48 mmol/l HbA1c) and normal FPG (< 5.6 mmol/l)

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GP activity and engagement

15,437 registered subjects for Project 1 (March 2017)

	Practices	Number contacted
Norfolk	97	102,277
Suffolk	31	33,705
NE Essex	7	8,577
Total	**135**	**144,559**

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Primary care electronic health record (EHR) search on SystmOne or EMIS in each of 135 East of England practices between 2011 - 2017

- Age ≥ 50 years with BMI ≥ 30 kg/m^2

- Age ≥ 50 years and BMI ≥ 25 kg/m^2 a and first degree family history of T2DM

  Prevalence 11.1 %

- Previous record of IFG , IGT or a fasting glucose of ≥ 6.1 - < 7.0 mmol/L

  Prevalence 1.7 %

- Previous record of HbA1c ≥ 42 - < 48 mmol/mol and fasting glucose ≥ 5.6 - < 6.1 mmol/L.

  Prevalence 2.7%

These 135 practices have data on 144,559 people at high risk stored as part of CRN – NDPS research contract (RISP) under a folder labelled NDPS

Distribution of glycaemic categories by HbA1c or fasting plasma glucose in 10,000 high risk participants screened for randomisation into NDPS in 135 E o E practices.

		< 42	≥ 42 – < 48
		Normal	NDH
< 5.6	Normal	6057 (60.6%)	990 (9.9%)
≥ 5.6 – < 6.1	IFG	968 (9.7%)	625 (6.3%)
≥ 6.1 – 6.9	IFG	306 (3.1%)	487 (4.9%)
≥ 7.0	T2DM	11 (0.1%)	70 (0.7%)
		7342 (73.4%)	**2172 (21.7%)**

Are these subgroups with NDH (42 – 48 mmol/mol) at same risk of T2DM ?

About a 3 – 4 fold difference in T2DM diabetes risk

Risk stratification based on additional fasting plasma glucose data is an attractive option

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Prevalence (%) of NDH and/or IFG by age band and BMI band in 10,000 subjects from East of England practices screened for NDPS

	BMI (kg/m2)	
Age (yrs)	> 25 - 30	> 30 - 35
50 -54	17	15
55 -59	19	21
60 - 64	25	22
65 -69	25	29
70 -74	37	24

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Short term regression and progression rates in a second baseline HbA1c sample in subjects with an abnormal first baseline HbA1c after a median of 40 days.

	Repeat baseline sample category		
Baseline category	**Normal**	**NDH**	**T2DM**
Normal (HbA1c < 42 mmol/mol)	268 (76.4%)	83 (23.6%)	0 (0%)
HbA1c ≥ 42 to < 48 mmol/mol)	312 (21.3%)	1047 (71.6%)	104 (7.1%)
Type 2 diabetes (≥ 48 mmol/mol)	1 (0.3 %)	82 (20.8%)	311 (78.9%)

- ✓ Very difficult to accurately quantify true risk of T2DM without paired baseline data as 25 – 33 % regress to normal after median 40 days at baseline

- ✓ Very difficult to accurately quantify true risk of T2DM on HbA1c data alone, when fasting glucose data is also an effective marker and extreme discordance .

- ✓ NDPS data allows decisions on NDPP capacity planning, prevalences, and risk stratification in East of England

- ✓ Most Norfolk/Suffolk/NE Essex practices have already searched and stored database searches for high risk groups.

- ✓ Population based strategies in addition to screen and treat approach

- ✓ NDPS largest current prevention trial, reports in 2018, and is properly powered to answer :

    - Outcomes of high intensity intervention in common unstudied NDH groups
    - Effect of additional use of lay trainers with T2DM to deliver intervention
    - Costs and interaction with UK primary care
    - Intervention in screen detected T2DM
    - Group working rather than 1:1

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