Evidence of the Effectiveness of Primary Prevention of type 2 diabetes

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Measuring human capital: a systematic analysis of 195 countries and territories, 1990–2016

Stephen S Lim, Rachel L Updike, Alexander S Kaldjian, Ryan M Barber, Krycia Cowling, Hunter York, Joseph Friedman, R Xu, Joanna L Whisnant, Heather J Taylor, Andrew T Leever, Yesenia Roman, Miranda F Bryant, Joseph Dieleman, Emmanuela Gakidou, Christopher J L Murray

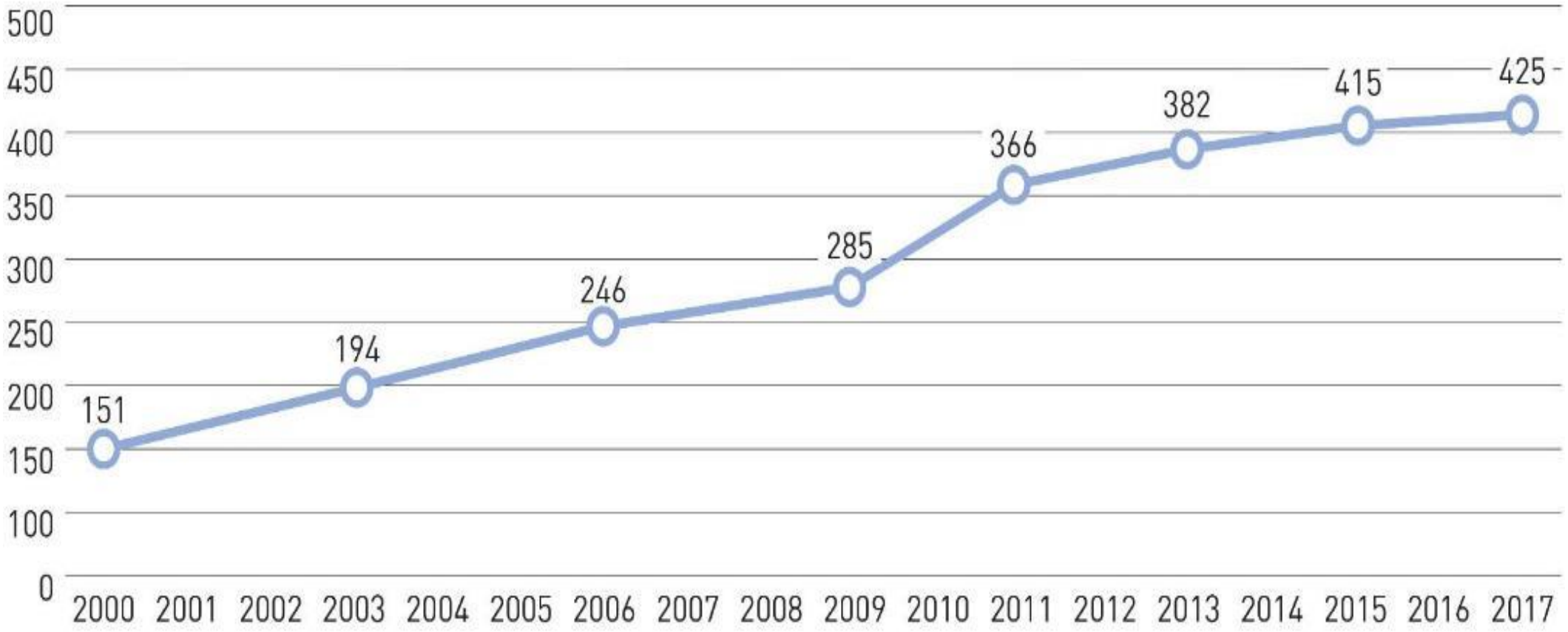
www.thelancet.com **Published online September 24, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31941-X**

Methods We generated a period measure of expected human capital, defined for each birth cohort as the expected years lived from age 20 to 64 years and adjusted for educational attainment, learning or education quality, and functional health status using rates specific to each time period, age, and sex for 195 countries from 1990 to 2016. We

Findings In 2016, Finland had the highest level of expected human capital of 28·4 health, education, and learning-adjusted expected years lived between age 20 and 64 years (95% uncertainty interval 27·5–29·2); Niger had the lowest expected human capital of less than 1·6 years (0·98–2·6). In 2016, 44 countries had already achieved more than 20 years of expected human capital; 68 countries had expected human capital of less than 10 years. Of 195 countries,

Diabetes around the world

The number of adults (20-79 years) with diabetes has tripled during the last 2 decades, millions



IDF: Diabetes Atlas 2017

DIABETES MELLITUS AND ITS PREVENTION.*

By *Rai* Koilas C. Bose, *Bahadur*, L.M.S.

It is indeed very difficult to trace out with any amount of certainty the period when Diabetes Mellitus was for the first time added to the nomenclature of our Indian diseases ; but there is evidence to show from record that it was not absolutely unknown to the practitioners of the Hindu system of medicine. The ancients gave the name Diabetes or *Bohumootra* (Polyuria) to a group of symptoms, the most prominent being augmented secretion of urine, thirst, dry skin, gradual emaciation and loss of strength. For want of a sufficient knowledge of Chemistry the Indian physicians could not isolate true Diabetes from simple Polyuria, and in their honest attempt to differentiate the disease they have blended it with diverse urinary diseases characterised by general weakness of the body.

betes lie in the liver, in the gastro-intestalin tract, and in the nervous centre. When one of these factors is involved Diabetes is only transient, and the sugar altogether disappears from the urine after the defect has been rectified. The term Glycosuria is implied to signify such temporary disorders, and the health does not suffer much from it. It may arise from certain error of diet. It may come on after an injury and independently of the food of the patient. Again, a small quantity of sugar may be occasionally detected in the urine of pregnant women. I know an instance where a hysterical lady when pregnant, used to pass an unusually large quantity of saccharine urine, but a few weeks after her delivery no trace of sugar could be had in the urine. During this temporary attack of Glycosuria no appreciable change was noticed in her health. The experiments of Mering and Minkoviski clearly demonstrated that the excision

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THE PREVENTION OF DIABETES MELLITUS

ELLIOTT P. JOSLIN, M.D.

BOSTON

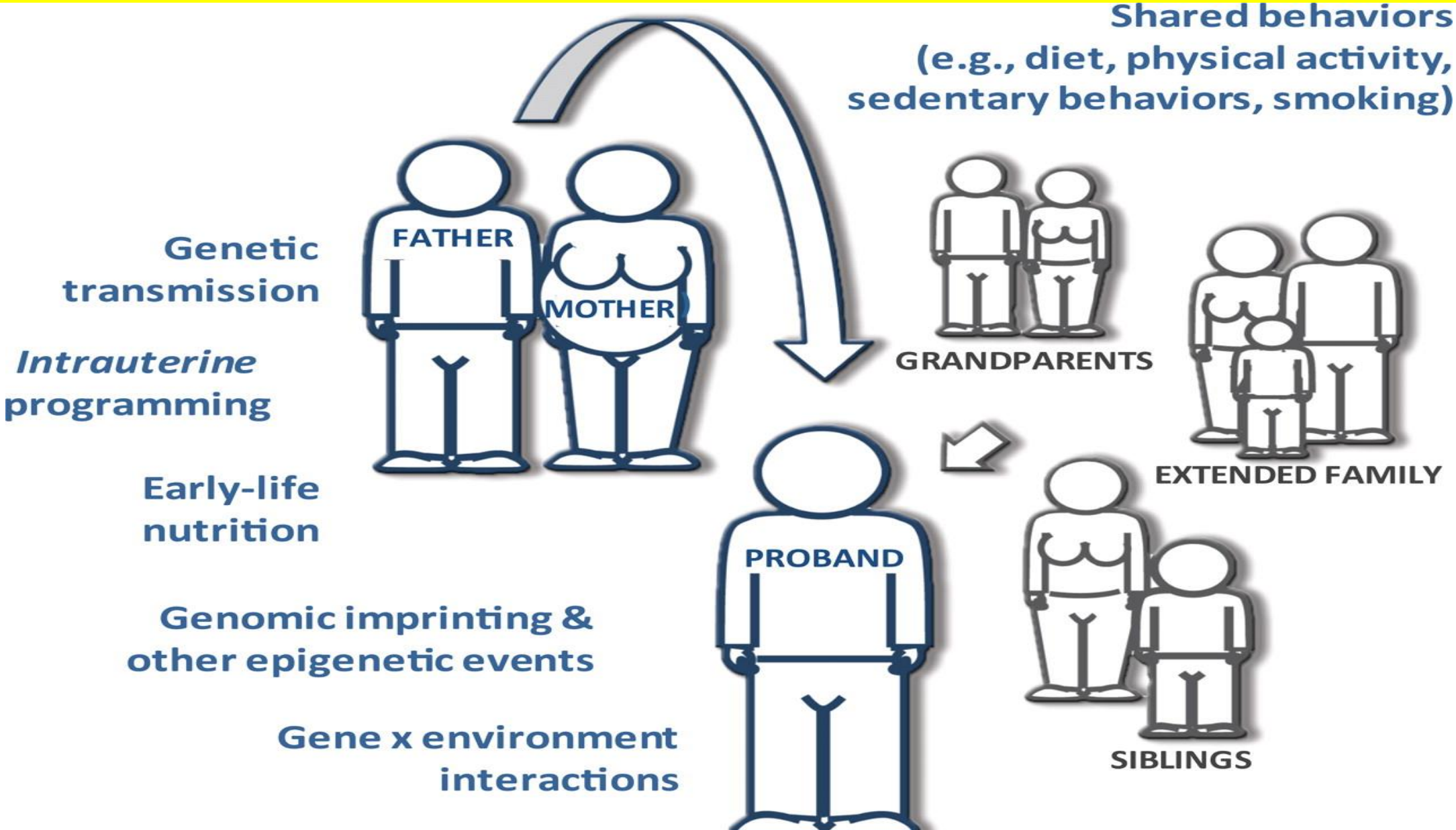
On the broad street of a certain peaceful New England village there once stood three houses side by side, as commodious and attractive as any in the town. Into these three houses moved in succession four women

of the United States was 10 per hundred thousand, and in 1915, 18 per hundred thousand. In the same period in Boston, it rose from 14 to 26 on the same basis. There are probably more than half a million diabetics in the United States. Therefore, it is proper at the present time to devote attention not alone to treatment, but still more, as in the campaign against typhoid fever, to prevention. The results may not be quite so striking or as immediate, but they are sure to come and to be important.

Necessary prerequisites for a successful disease prevention

1. Commonly agreed diagnostic definition for the disease;
2. Adequate knowledge about the risk factors for the disease;
3. Good understanding of the natural history of the disease;
4. Acceptable and efficient methods to identify high-risk individuals in the population;
5. Acceptable and efficient methods to influence the modifiable risk factors of the disease;
6. Demonstration in an intervention study setting that disease rates are reduced following the risk factor modification.
7. Development a population approach for the control of major risk factors for the disease by implementing policies outside the health sector.

The complex interplay between genes, shared environment, shared behaviors and epigenetic effects



Type 2 diabetes risk factors

Risk markers

- Age
- Family history, gene markers
- Gestational diabetes
- Delivery of macrosomic baby
- Low SES
- Low birth weight
- Hypertension
- Metabolic syndrome
- Previous CVD
- Polycystic ovary syndrome, PCOS
- Non-alcoholic fatty liver disease, NAFLD

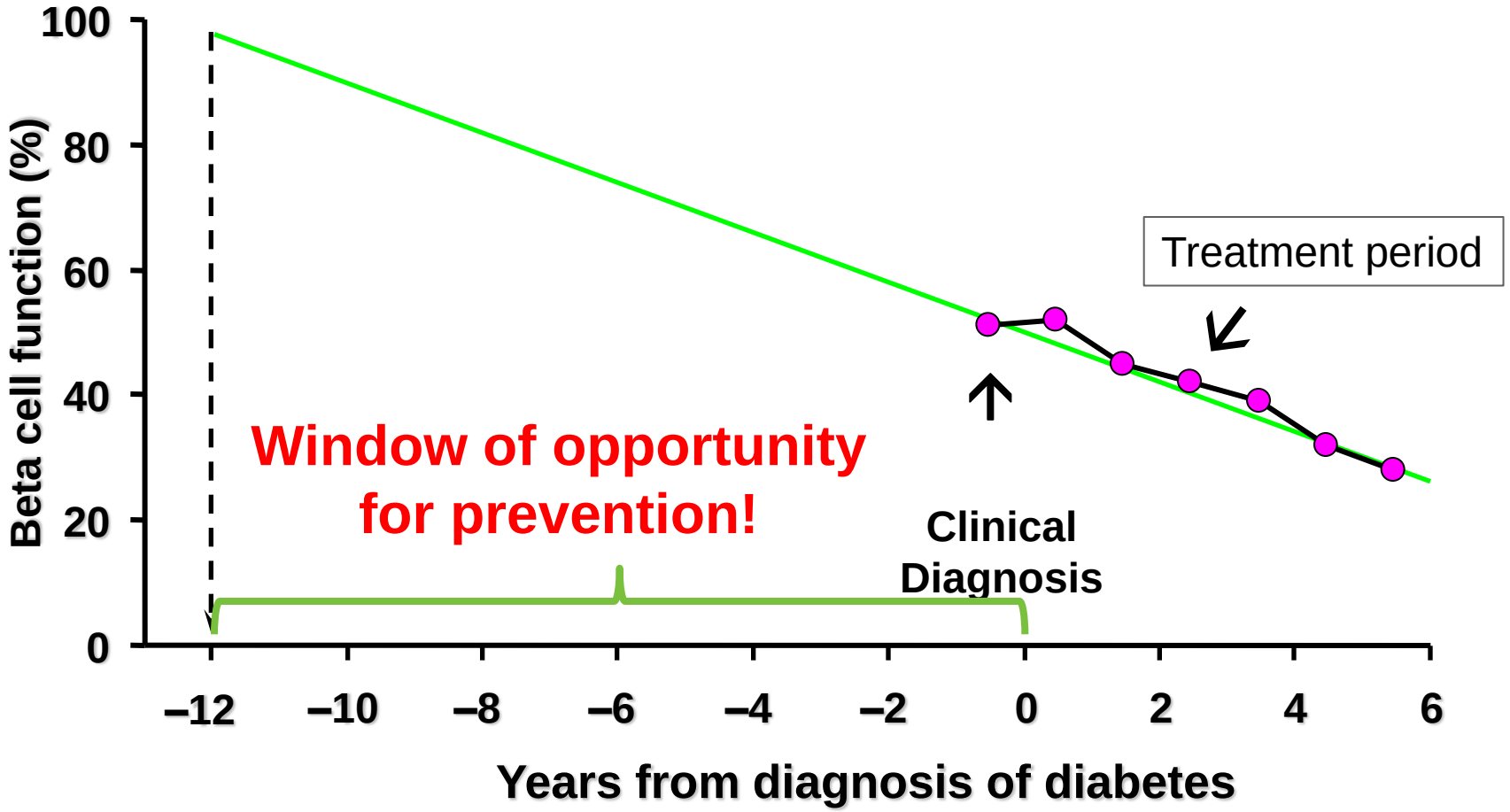
Modifiable risk factors

- Overweight / obesity
- Abdominal adiposity
- Low physical activity
- Smoking
- Unhealthy diet

Possibly modifiable risk factors

- Sleep deprivation
- Distress and depression
- Persistent organic pollutants (e.g. pesticides, solvents, pharmaceuticals)
- Microbiota

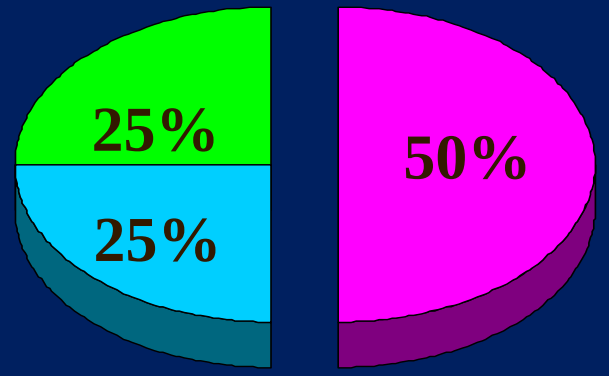
Type 2 diabetes is a progressive disease of pancreatic beta cell dysfunction: UKPDS data extrapolation



Adapted from UKPDS 16. Diabetes 1995

Natural History of Impaired Glucose Tolerance: Dysglycemia is a progressive disorder

IGT (prediabetes)



Science provides facts, but it does not change behavior or culture

Hierarchy of *Scientific Evidence* for Best Practices

- **Meta-Analyses and Systematic Reviews of Trials**
- **Randomized controlled trials**
- **Non-randomized, controlled intervention studies**

Best

- **Meta-analyses of observational studies**
- **Observational studies**
- **Uncontrolled evaluation of existing programs**
- **Anecdotal experience**
- **Intuition and common sense**

Promising

Archie Cochrane –

EFFECTIVENESS & EFFICIENCY

Nuffield Provincial Hospitals Trust 1973

3 Key Questions about any intervention:

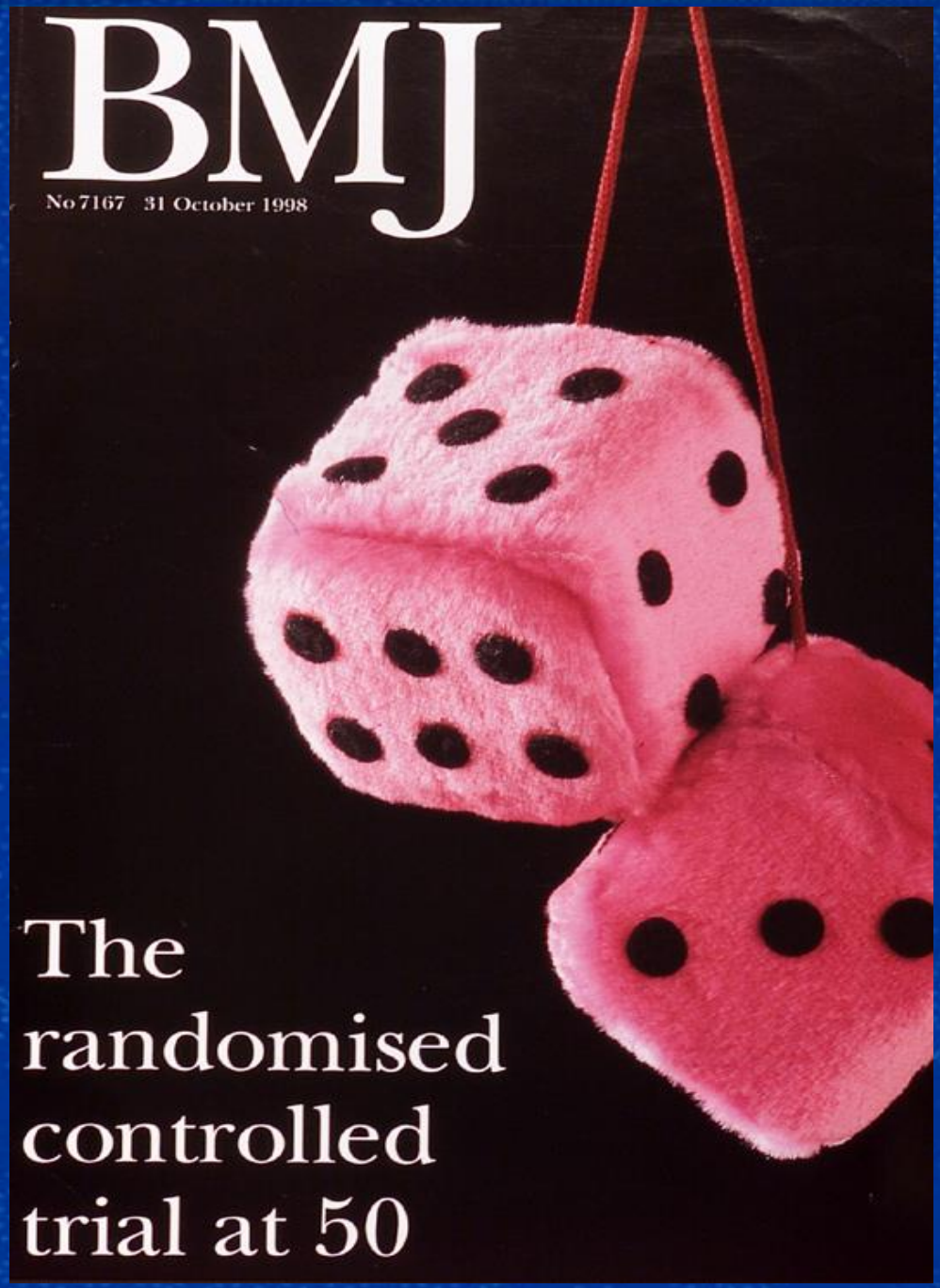
1) Can it work ?

2) Does it work in practice ?

3) Is it worth it ?

The Randomised Clinical Trials (RCT) –

a quite recent development



WHAT IS IT?

- It is an experimental epidemiological method.
- It is an interventional study on individuals, usually on patients or people at high risk.

WHAT ARE ITS OBJECTIVES?

- **Intervention trials determine whether experimental treatments or trials are safe and effective under controlled environments**
- **Observation trials address health issues in large groups of people in natural settings.**

WHAT IS IT?

A research study in human volunteers to answer a specific health question

(U.S National Library of Medicine)

Why Start a Clinical Trial?

1) To Answer an Important Question: Proof of Concept

2) To Answer it Clearly – which needs a
Lot of CLEARLY DEFINED End Points

3) To Avoid Bias, therefore Randomisation

4) To Obtain Results which are
Widely Applicable in Clinical Practice

5) To check on potential Observational study Bias

WHY THEY ARE DONE?

1. As they provide better evidence of the effect or the outcome (e.g. safety) that cannot be obtained with any other observational method.

2. The random variation is minimized and bias is controlled, hence more valid and their results speak truth.

WHY THEY ARE DONE?

3. Enjoying maximum confidence just like any other scientific laboratory experiment
4. Providing maximum amount of assurance
5. Fastest and safest way to find treatments that work in people and ways to improve health

The proof of concept for prevention of type 2 diabetes –

Randomized Controlled Trials (RCT)

Chinese Da Qing Study in people with Impaired Glucose Tolerance (IGT)

STUDY GROUP	Diabetes incidence	Relative Risk
Control group	15.7%	1.00
Diet	10.0%	0.64
Exercise	8.3%	0.53
Diet & exercise	9.6%	0.61

Study participants were not randomly allocated to different groups; 35 clinics were randomised

Pan XR et al. Diabetes Care 1997;20:537

DPS: The Finnish Diabetes Prevention Study

The main aim:

To determine whether lifestyle intervention of overweight, middle-aged subjects with impaired glucose tolerance (IGT) will prevent or delay the development of type 2 diabetes

Study subjects:

- 522 subjects with IGT in two oral glucose tolerance tests
- Age 40–65 years, mean age 55 years
- BMI > 25 kg/m^2
- Randomization to standard care control group or intensive lifestyle intervention group
- Stratified randomisation by sex, centre and 2-h PG (< 9 vs ≥ 9 mmol/l)

N Engl J Med 2001; 344:1343

DPS: lifestyle goals

➢Weight reduction	> 5%
➢Fat intake	< 30 E%
➢Saturated fat intake	< 10 E%
➢Fibre intake	≥ 15 g/1000 kcal
➢Physical activity	> 30 min/day

Intervention group

- Individually tailored diet based on 3-day food diaries
- 7 dietary counselling sessions during the first year, every 3 months thereafter
- Free-of-charge gym

Control group

- General advice about healthy diet and exercise habits
- No individualised counselling

E, energy

Lindström et al. *Diabetes Care* 2003; 26:3230–6

Diabetes Prevention Program (DPP) -USA

Subjects

- 3400, > 25 years old, 45% ethnic minority
- IGT with fasting plasma glucose > 5.6 mmol/L
- Median follow up 3 years

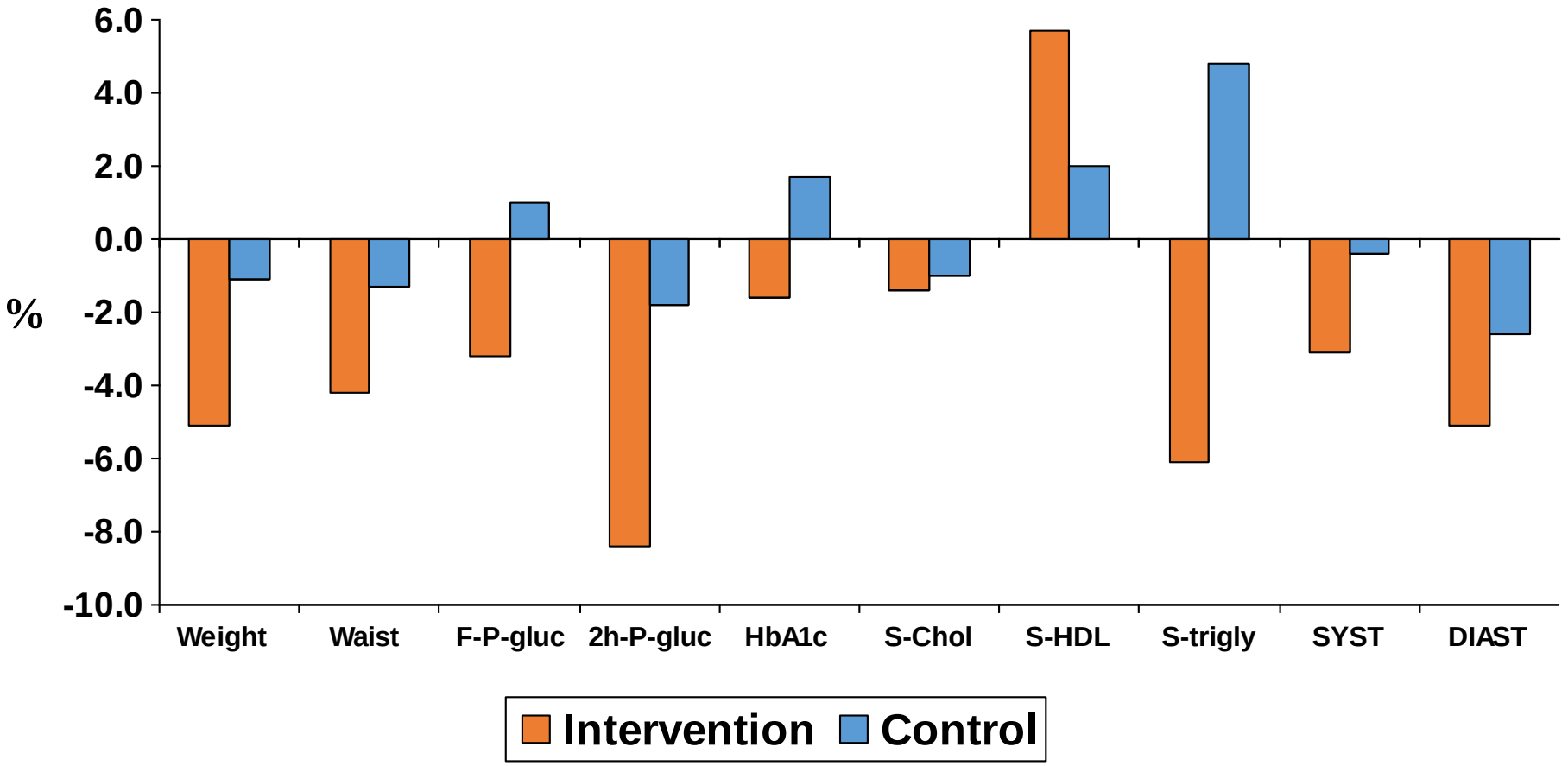
Interventions

1. Intensified diet and exercise lifestyle (1079 patients)
2. Metformin 1700 mg per day (1073 patients)
3. Placebo tablet (1082 patients)

Risk of false positive

- If one carries out ***10*** interim analyses the chance of at least one analysis showing a treatment difference significant at the *5%* level increases to ***0.19*** even if the treatments are truly equally effective.
- Stopping rules defined beforehand.
- Intention-to-treat (ITT) analysis
- Statistical analysis plan should be prepared beforehand

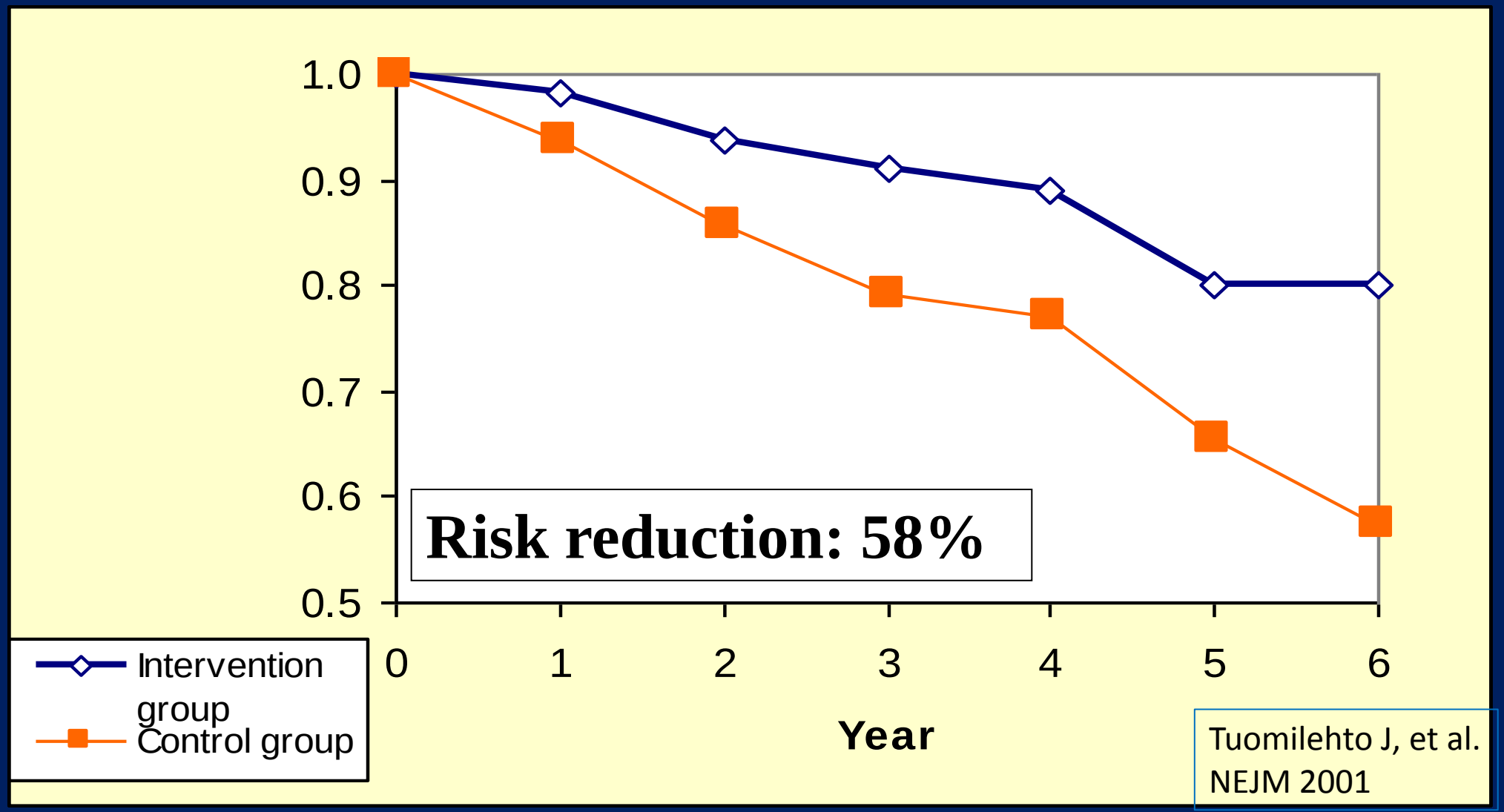
Changes (%) in the components of metabolic syndrome with lifestyle intervention: ALL IMPROVED!
From baseline to year 1 - DPS



DPS - Interim analysis of end-points

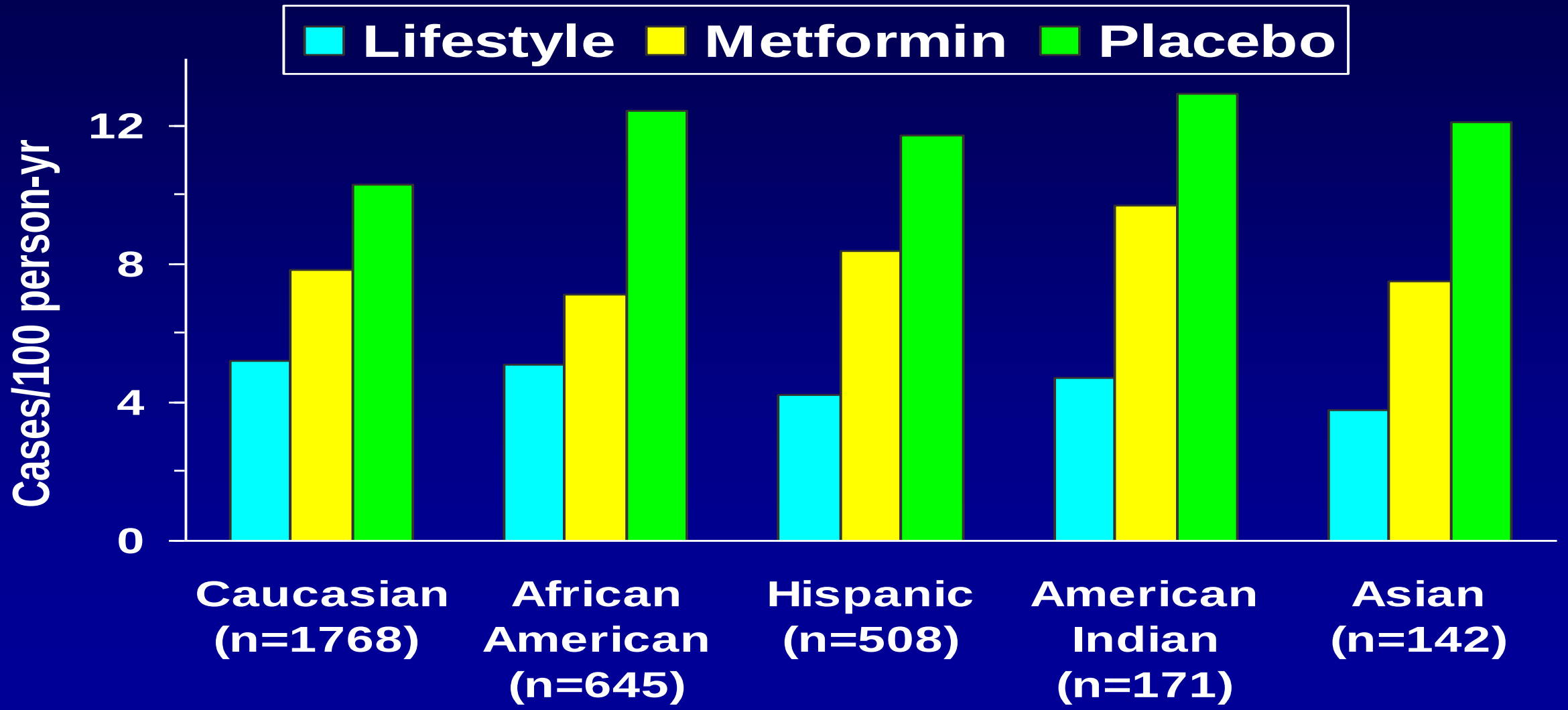
- The study was estimated to last for 6 years.
- 160 cases of diabetes was expected to occur.
- An interim analysis by randomization group was planned when 80 cases of diabetes had been accumulated.
- The analysis was carried out by an independent statistician .
- The median follow-up time at the time of the interim analysis was 3.2 years (range 1-6 years)

Reduction of diabetes incidence by lifestyle intervention – Finnish Diabetes Prevention Study (DPS)



Is Finland different, or just happy?

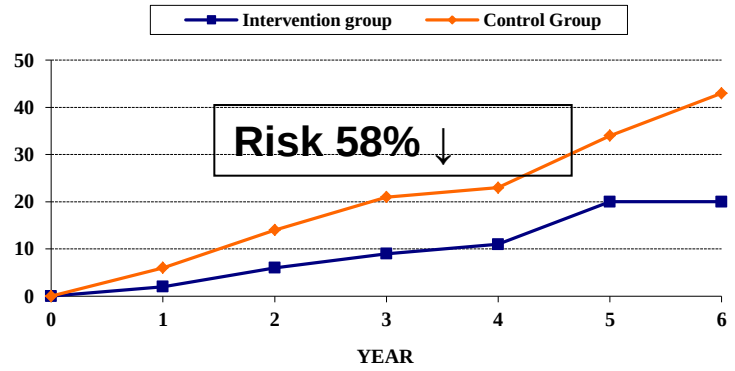
Diabetes Incidence Rate in US DPP was reduced by 58%



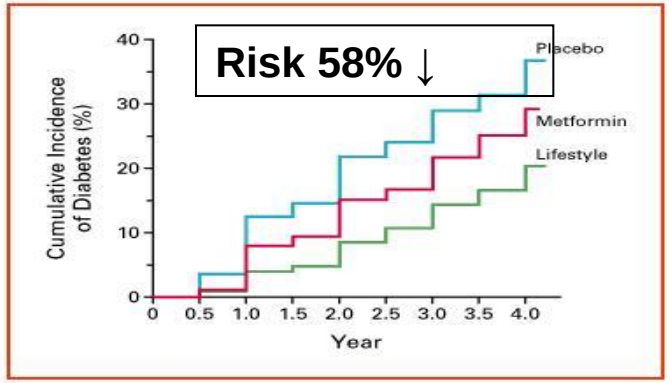
NEJM 2002

Prevention of T2D by Lifestyle Management: The Evidence from proof-of-concept trials in people with IGT

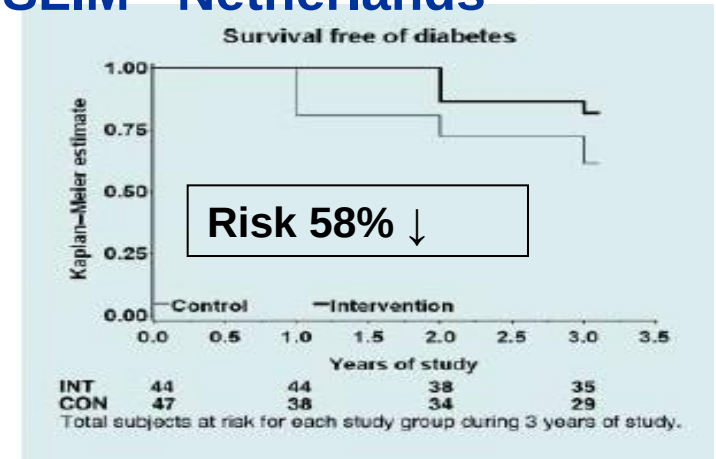
DPS - Finland



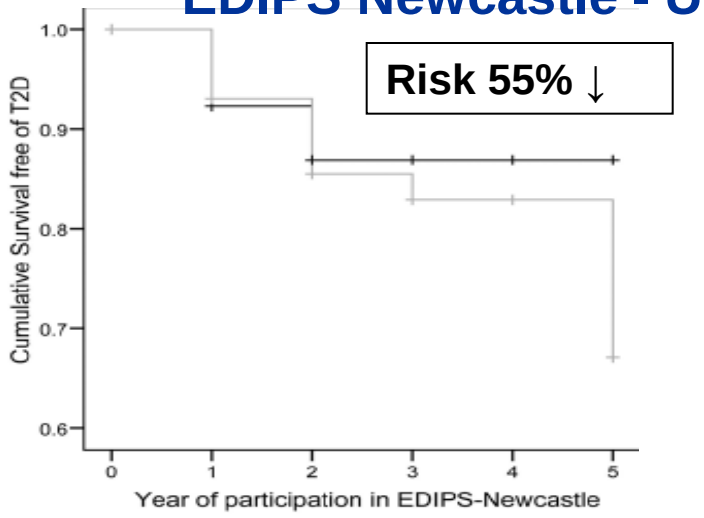
DPP - USA



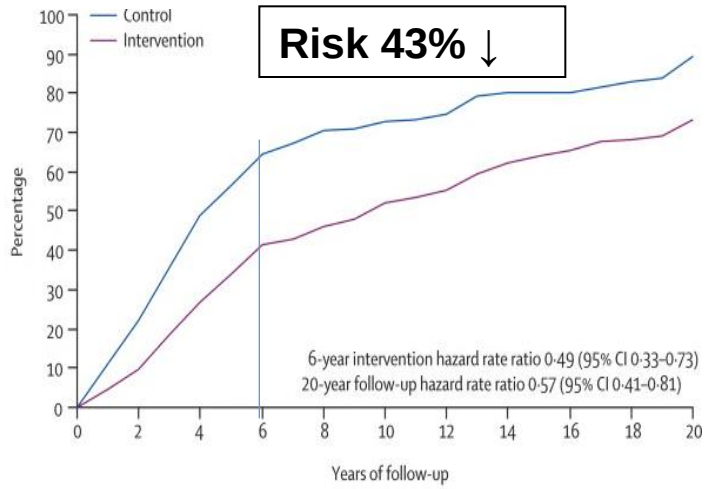
SLIM - Netherlands



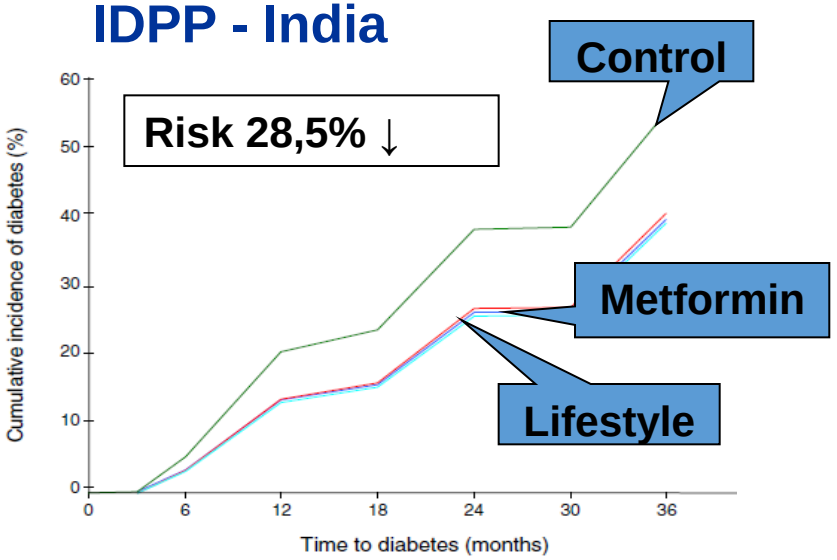
EDIPS Newcastle - UK

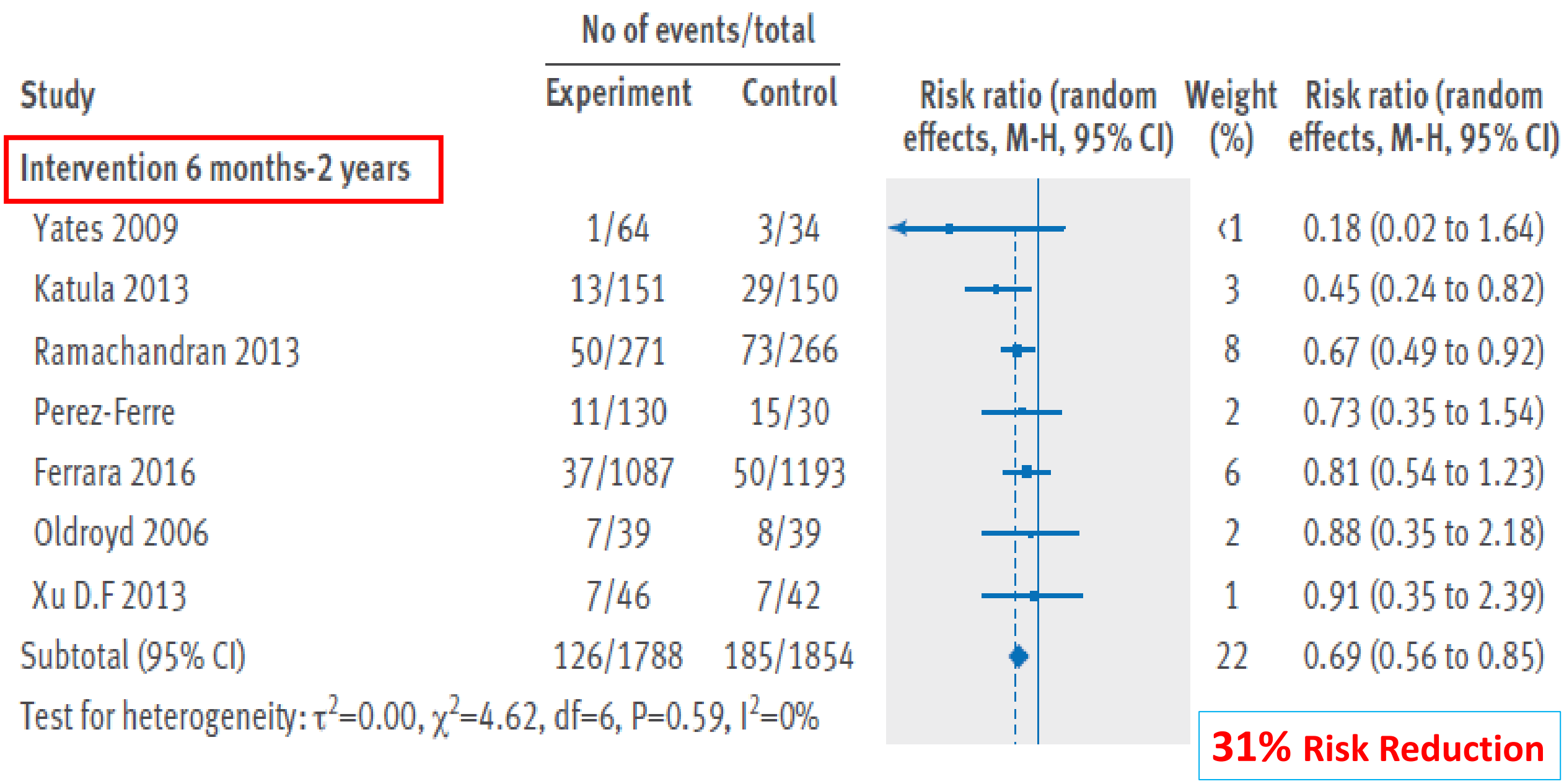


Da Qing - China



IDPP - India





Barry E, et el. *BMJ* 2017;356:i6538

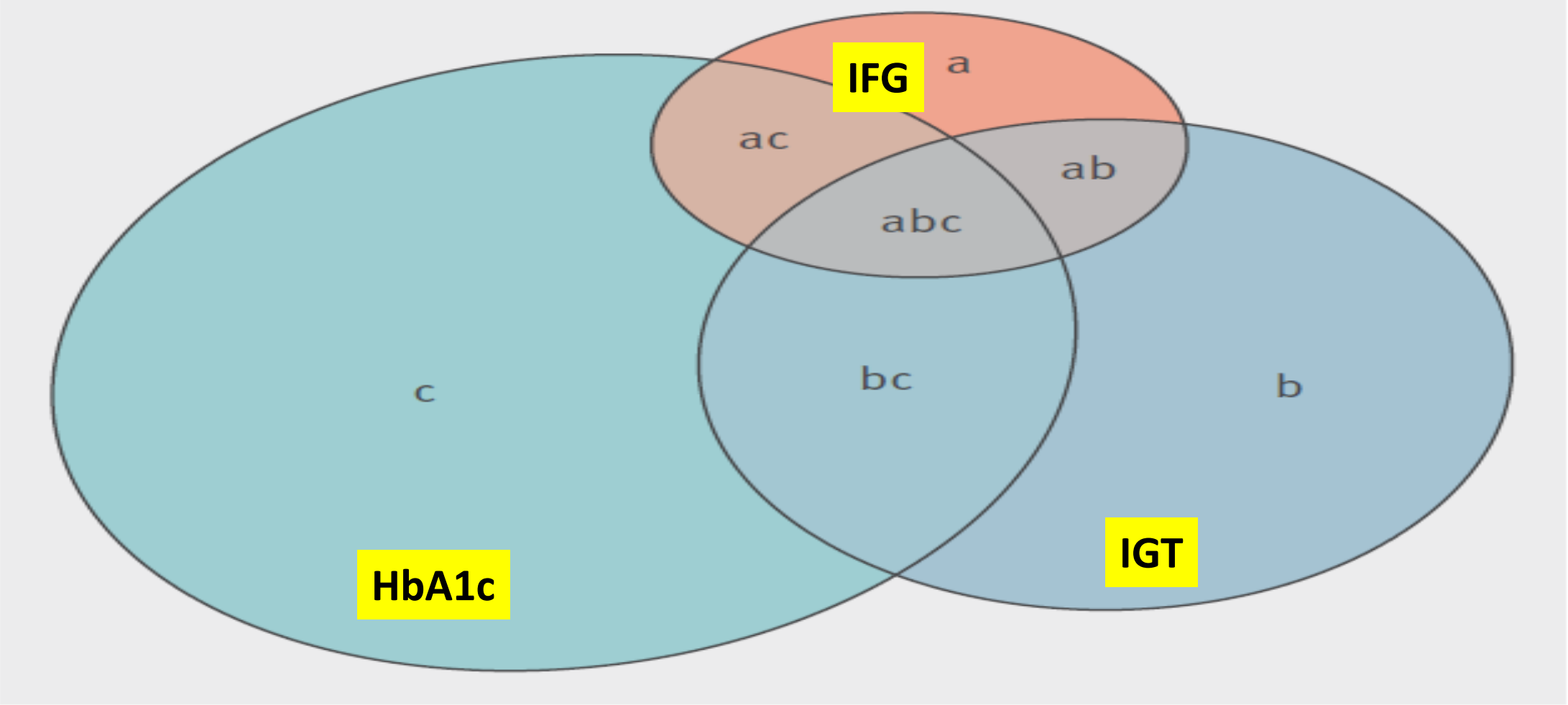


Fig 4 | Prevalence of pre-diabetes by diagnostic test with IEC and WHO criteria, showing overlap with all three tests. Prevalence of pre-diabetes was 27%. Of those with abnormal results, a=4.7% isolated IFG; b=24.4% isolated IGT; c=47.8% isolated HbA_{1c}; ab=2.9% IFG+IGT; ac=4.1% IFG+HbA_{1c}; bc=12.2% IGT+HBA_{1c}; abc=3.9% IGT+IFG+HbA_{1c};

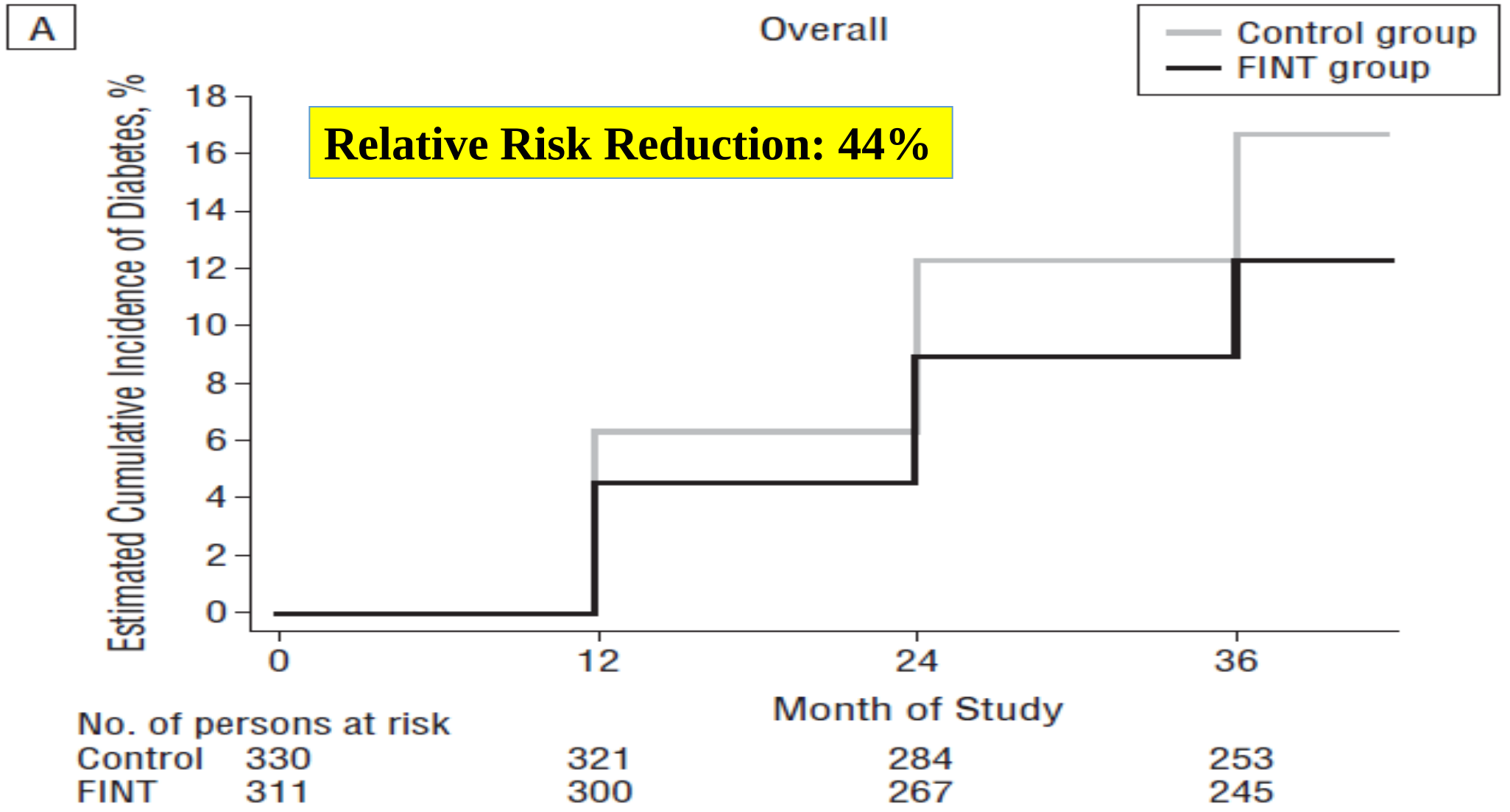
Will lifestyle intervention be similarly effective in people with impaired fasting glucose (IFG)?

Lifestyle Modification and Prevention of Type 2 Diabetes in Overweight Japanese With Impaired Fasting Glucose Levels

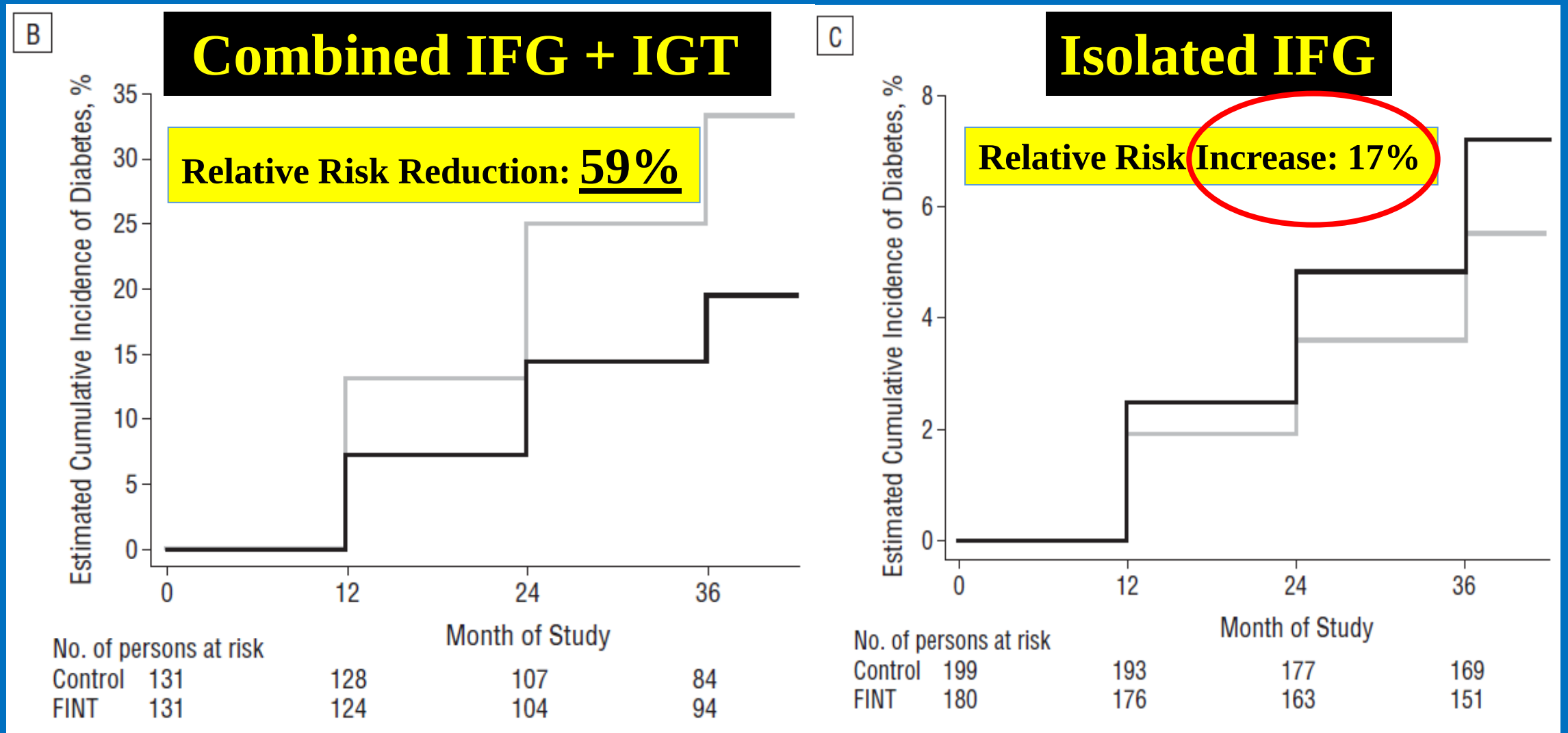
Toshikazu Saito, MD, PhD; Makoto Watanabe, MD, PhD; Junko Nishida, MD; Tomono Izumi, BA; Masao Omura, MD, PhD; Toshikazu Takagi, MD; Ryuzo Fukunaga, MD, PhD; Yasutsugu Bandai, Naoko Tajima, MD, PhD; Yosikazu Nakamura, MD, MPH, FFPH; Masaharu Ito, MD; for the Zensharen Study for Prevention of Lifestyle Diseases Group

Arch Intern Med. 2011;171(15):1352-1360

Zensharen Study – T2D incidence in the control and frequent intervention (FINT) groups



Zensharen Study – effect of the frequent intervention (FINT) on T2D incidence was not seen in people with IFG



Diabetes Prevention: Results From the D-CLIP Randomized Controlled Trial

Mohammed K. Ali,[1] K.M. Venkat Narayan, and Viswanathan Mohan[2]

Diabetes Care 2016;39:1760–1767 | DOI: 10.2337/dc16-1241

	IGT + IFG	Isolated IGT	Isolated IFG
Risk reduction with lifestyle intervention compared with the control group	**36%**	**31%**	**12%**
Need for additional **metformin**	**83%**	**51%**	**77%**

Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes?

K. Færch · K. Borch-Johnsen · J. J. Holst · A. Vaag

Diabetologia (2009) 52:1714–1723

- **Isolated IFG:** reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, altered glucagon-like peptide-1 secretion and inappropriately elevated glucagon secretion.
- **Isolated IGT:** reduced peripheral insulin sensitivity, near-normal hepatic insulin sensitivity, progressive loss of beta cell function, reduced secretion of glucose-dependent insulinotropic polypeptide and inappropriately elevated glucagon secretion.
- **Combined IFG/ IGT:** severe defects in both peripheral and hepatic insulin sensitivity as well as a progressive loss of beta cell function.

Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and trea of type 2 diabetes?

K. Borch-Johnsen · J. J. Holst · A. Vaag

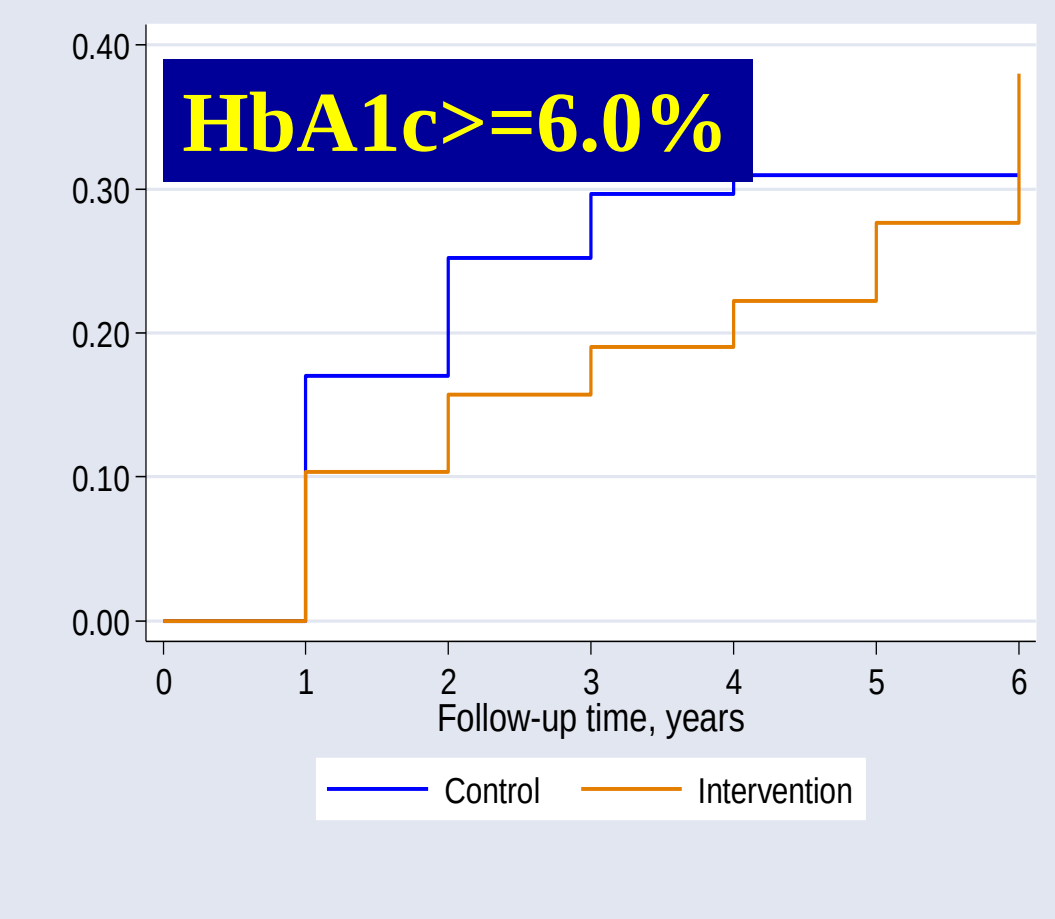
(2009) 52:1714–1723

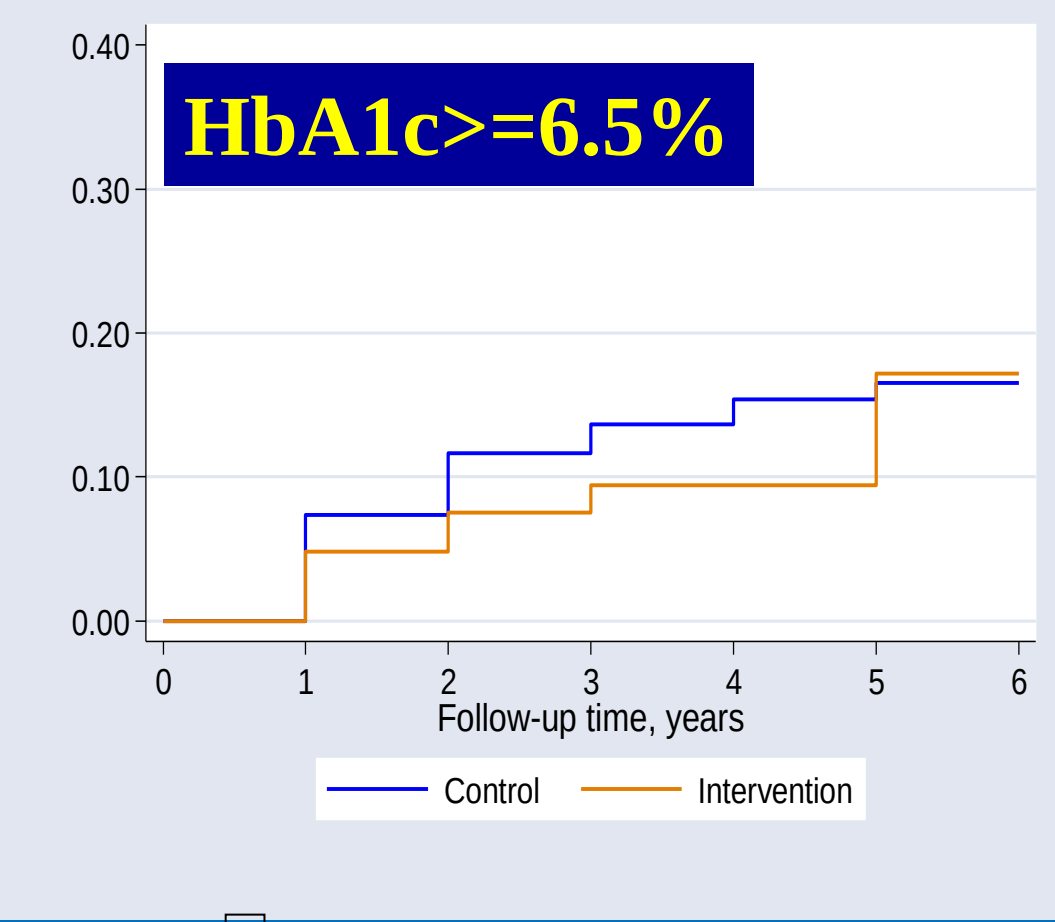
Elevated HbA1c does not tell anything about pathophysiology or aetiology of diabetes!

- **Isolated IFG:** reduced itivity, stationary beta cell dysfunction and/or chronic lo ltered glucagon-like peptide-1 secretion and inappropriately eleva tion.
- **Isolated IGT:** reduced peripheral insulin rmal hepatic insulin sensitivity, progressive loss of beta cell functio of glucose-dependent insulinotropic polypeptide and inappropr cagon secretion.
- **Combined IFG/ IGT:** severe defects in both peripheral and he in sensitivity as well as a progressive loss of beta cell function.

Can we use HbA1c for the outcome assessment (diagnosis of diabetes) in diabetes prevention programmes?

Incidence of T2D as HbA1c>=6.0 and HbA1c>=6.5 in the DPS study: TOO INSENSITIVE





The sensitivity of the HbA_{1c} ≥6.5% compared with diagnosis based on 2 x OGTT:

35% (95% CI 24% - 47%) among women

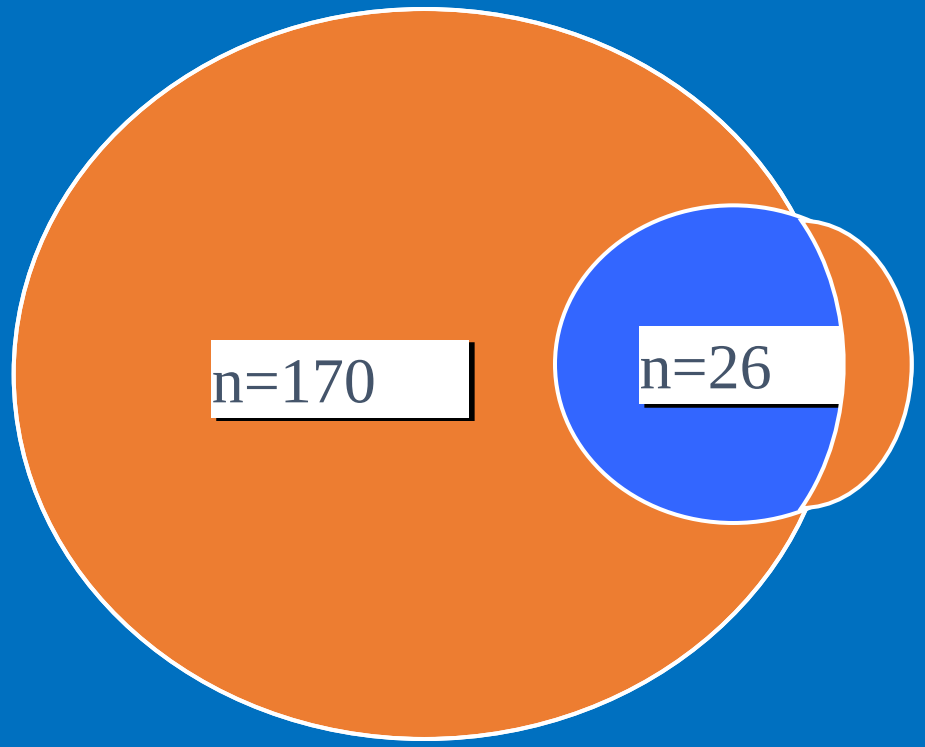
47% (95% CI 31% - 64%) among men

Pajunen et al. Diabetic Med, 2011

Poor impact of the A1C as a diagnostic criterion for T2D in the prospective DE-PLAN-CATALONIA cohort - people with FINDRISC ≥12 points

N=2287

***Overlap index* = 12,9%**



WHO-OGTT

DM: n=196

A1C ≥ 6.5%

DM: n=31

Costa et al. Diabetic Med 2011; 28: 1234-7

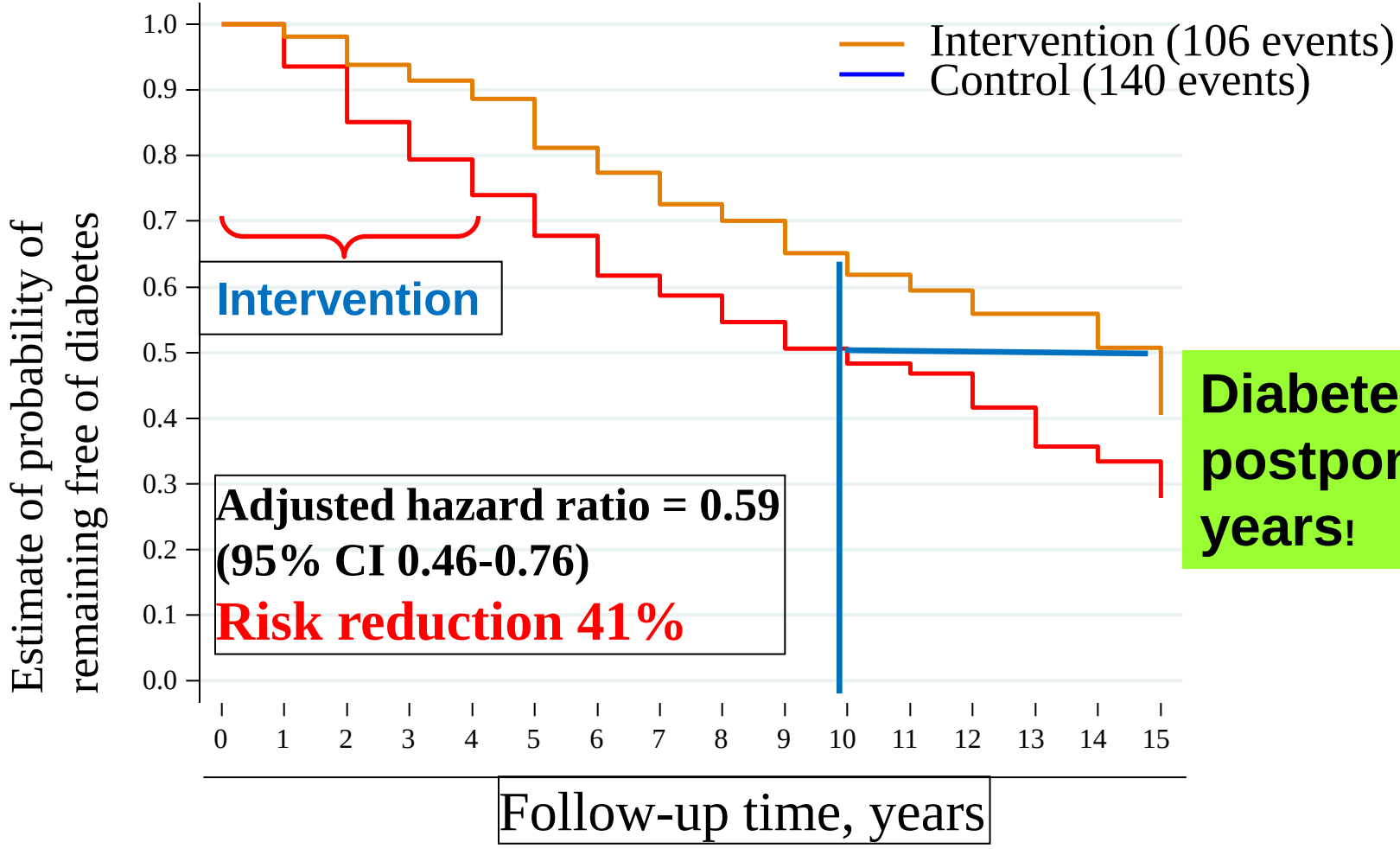
3. Prevention or Delay of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2019* **ADA**

Diabetes Care 2019;42(Suppl. 1):S29–S33 | https://doi.org/10.2337/dc19-S003

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.1**), is recommended to guide providers on whether performing a diagnostic test for prediabetes (**Table 2.5**) and previously undiagnosed type 2 diabetes (**Table 2.2**) is appropriate (see Section 2 "Classification and Diagnosis of Diabetes"). Those determined to be at high risk for type 2 diabetes, including people with A1C 5.7−6.4% (39−47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose, are ideal candidates for diabetes prevention efforts. Using A1C to screen for prediabetes may be problematic in the presence of certain hemoglobinopathies or conditions that affect red blood cell turnover. See Section 2 "Classification and Diagnosis of

How long will the effect of the lifestyle intervention last to prevent diabetes?

The difference in diabetes incidence between the original intervention and control groups remained over 13 years (median follow-up 9 years) - DPS



Diabetes onset postponed by 5 years!

Adjusted HR:
for sex, age, 2h glucose and BMI at baseline.

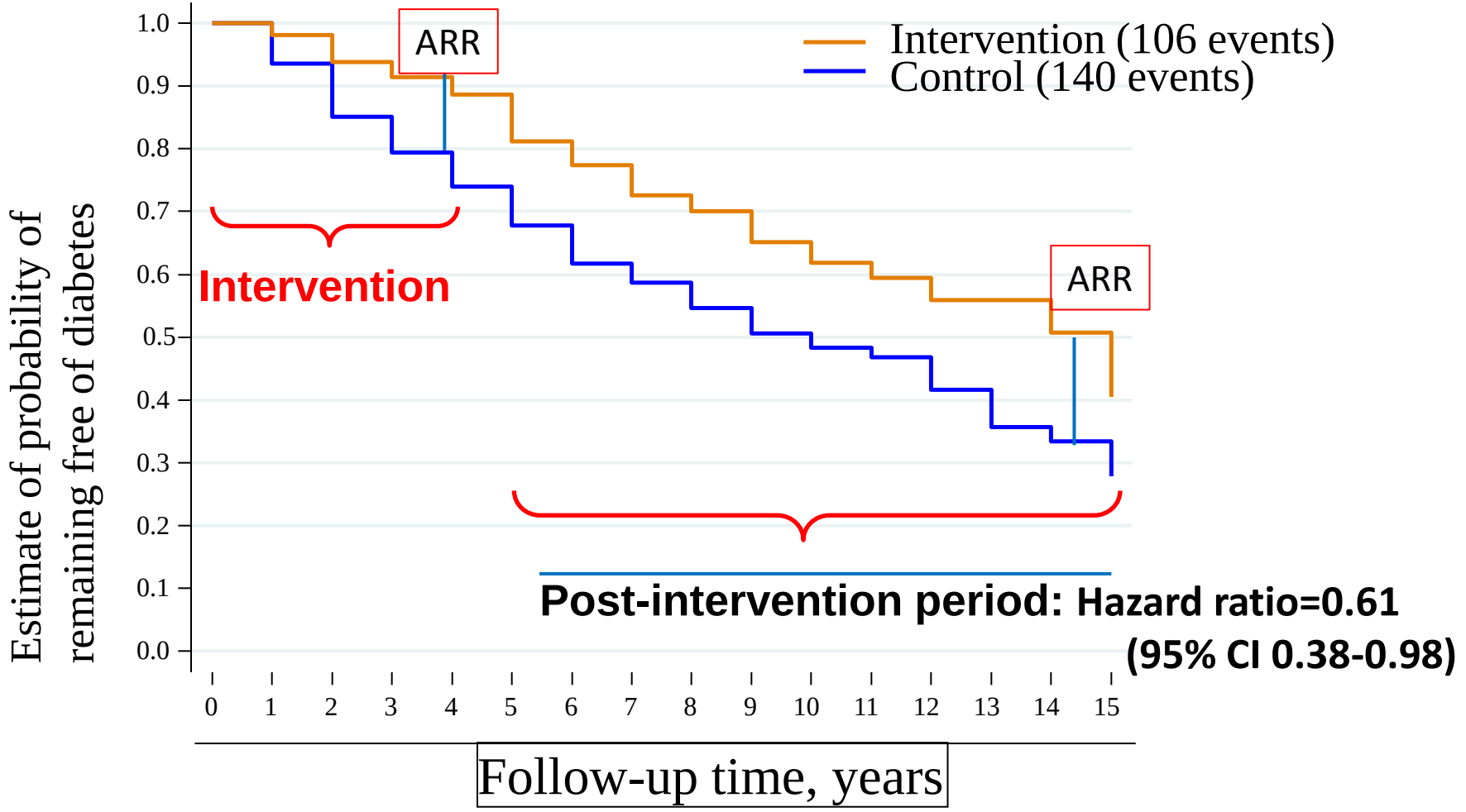
Lindström et al. Diabetologia. 2013

Table. Random Effects Meta-analyses Exploring RR for Diabetes Among LSM and Medication Studies After Treatment Withdrawal

JAMA Intern Med. doi:10.1001/jamainternmed.2017.6040
Published online November 6, 2017.

Source	Intervention	Active Intervention, years	End of Active Intervention, RR (95% CI)	Follow-up[a]	End of Follow-up, RR (95% CI)
LSM Trials					
Swinburn et al,[40] 2001	Reduced-fat diet	1.0	0.76 (0.25-2.34)	5.0 y	0.70 (0.26-1.88)
DPP,[33,34] 2002, 2009[b]	Diet and physical activity	2.8	0.48 (0.41-0.58)	5.7 y	0.68 (0.63-0.73)
DPS,[35,36] 2001, 2013	Diet and physical activity	4.0	0.44 (0.29-0.68)	9.0 y	0.63 (0.54-0.73)
Da Qing,[37,38] 1997, 2008	Diet and physical activity	6.0	0.68 (0.54-0.85)	9.4 y	0.86 (0.81-0.92)
Pooled estimate			0.55 (0.43-0.70)		0.72 (0.60-0.86)

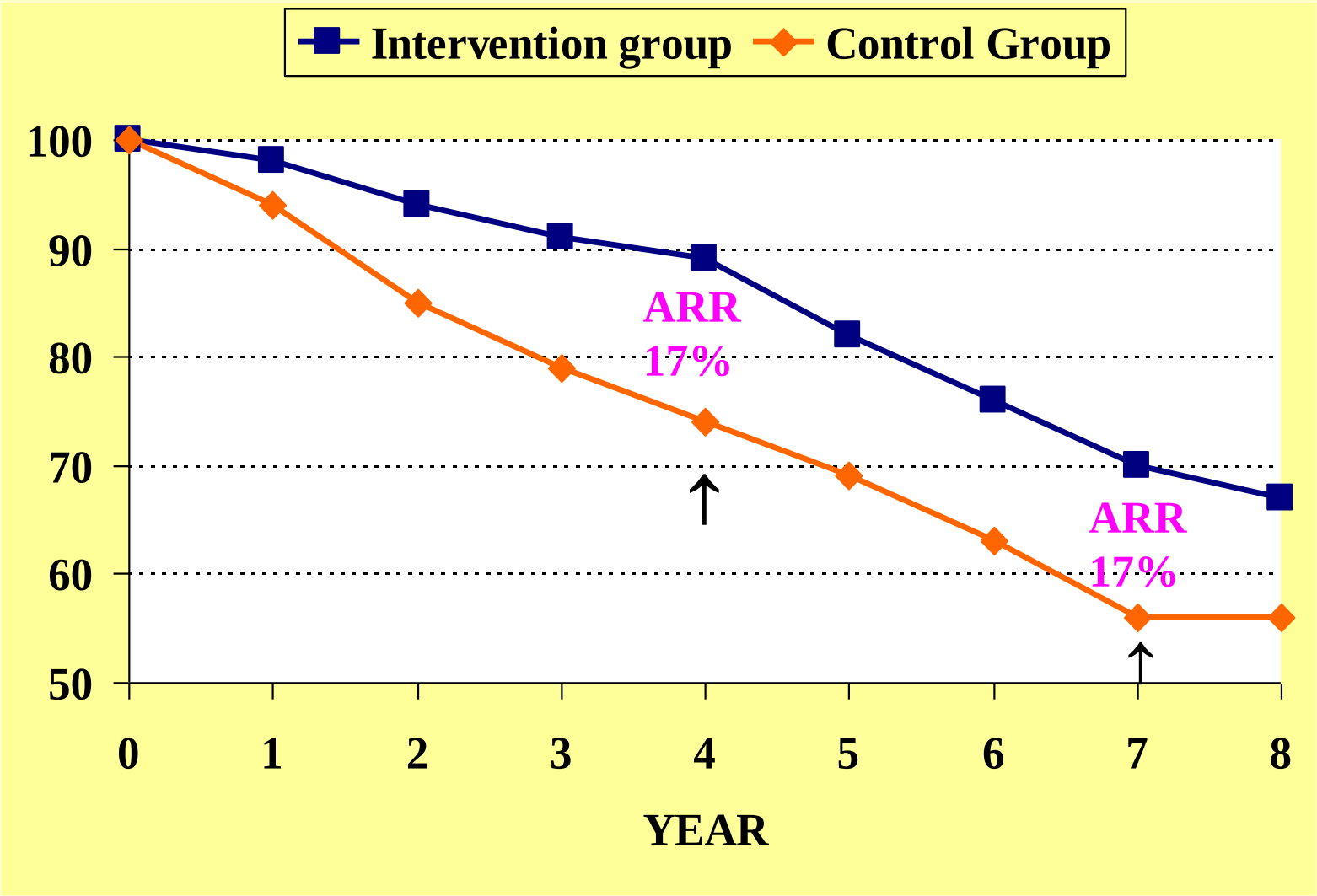
The ABSOLUTE RISK DIFFERENCE (ARR) in T2D incidence between groups did not diminish, but increased during the post-intervention follow-up period



Adjusted HR:
for sex, age, 2h glucose and BMI at baseline.

Lindström et al. Diabetologia. 2013

DPS: Development of diabetes in the intervention and control groups:



Relative Risk Reduction (RRR) during trial:
Rate at 4 years: IG 10%
CG 27%
RRR = 10/27 = 63.0%

Relative Risk Reduction (RRR) during extension:
Rate at 7 years: IG 29%
CG 46%
RRR = 29/46 = 37.0%

Numbers needed to treat (NNT)

DPS original trial period:

Absolute risk of diabetes:

32/1000 person-years intervention group

78/1000 person-years control group.

Absolute Risk Reduction (ARR): 78 - 32 = 46/1000 person-years

NNT = 1/ARR

= (1 x 1000)/46 = 21.7

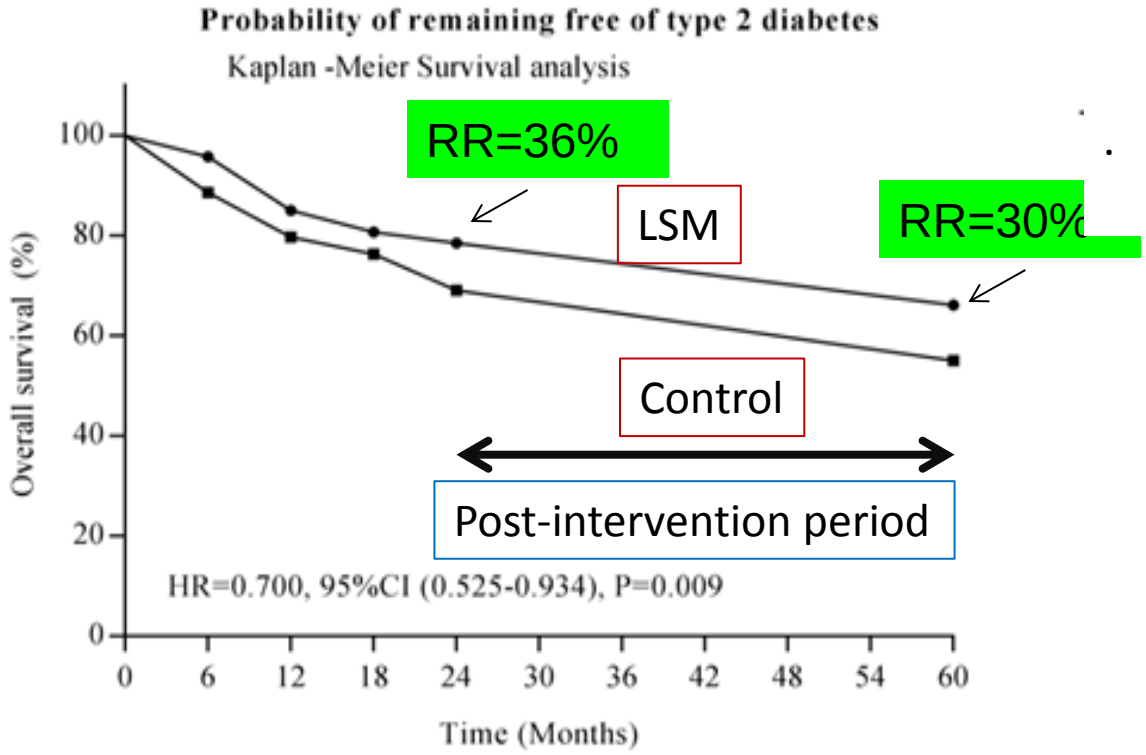
Thus,

22 people with IGT need to be treated for one year

with a life-style intervention to prevent one case of diabetes;

5 people with IGT need to be treated for 4 years

Sustained effect of lifestyle modification (LSM) in the SMS study in prevention of diabetes in Asian Indians



Cumulative Incidence of diabetes n (%)

Group	6 months	12 months	18 months	24 months	60 months
Control (n=236)	27 (11.4)	48 (20.3)	56 (23.7)	73 (30.9)	106(44.9)
Intervention(n=233)	10 (4.3)	35 (15.0)	45 (19.3)	50(21.5)	79 (33.9)

HR - Hazard Ratio

Nanditha et al, DRCP:142 (2018) 213–221

Nanditha et al, accepted for publication in JCD

ADHERENCE:

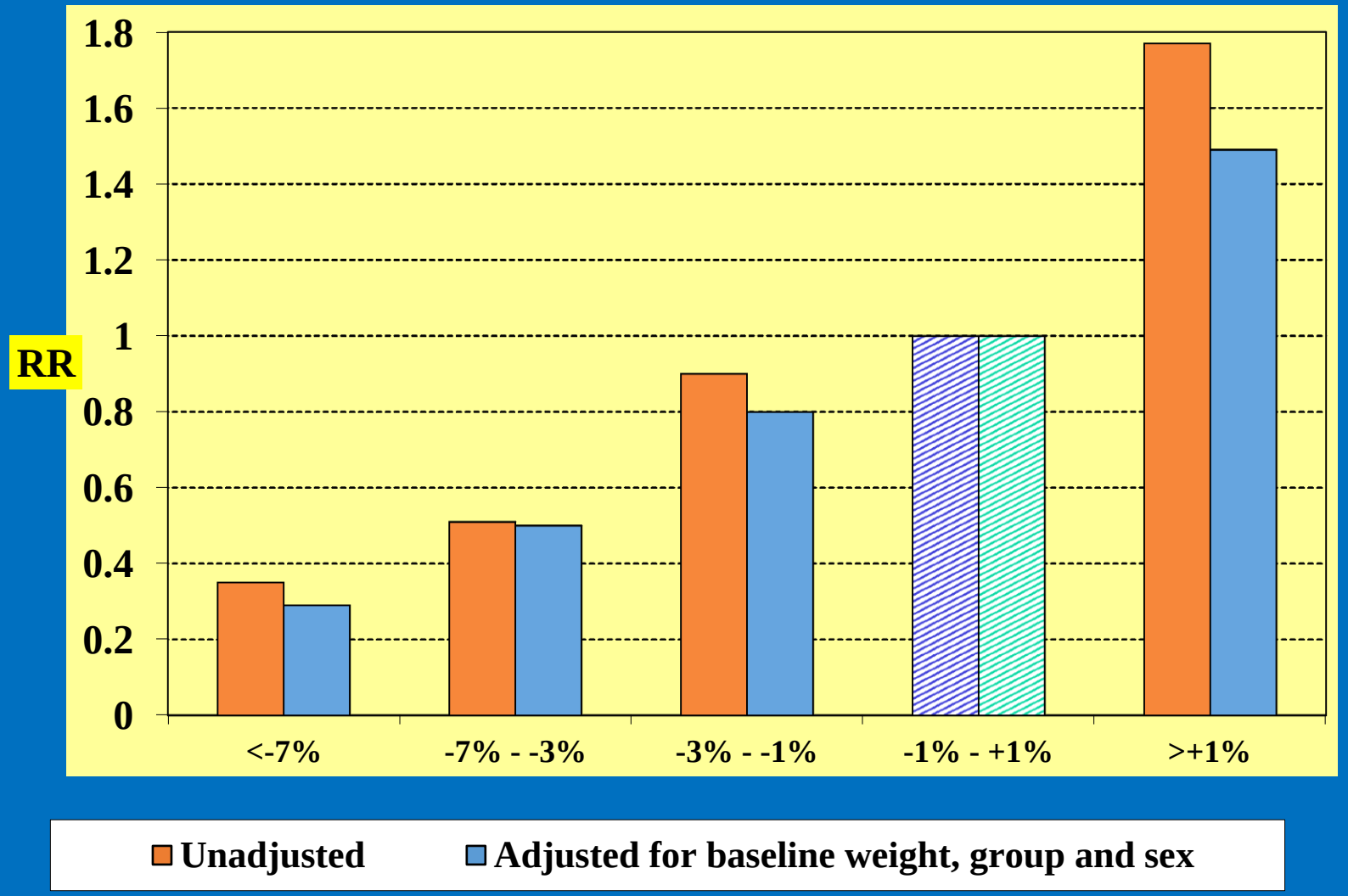
A drug does not work, if not taken.

Lifestyle intervention does not work, if people do not comply with intervention.

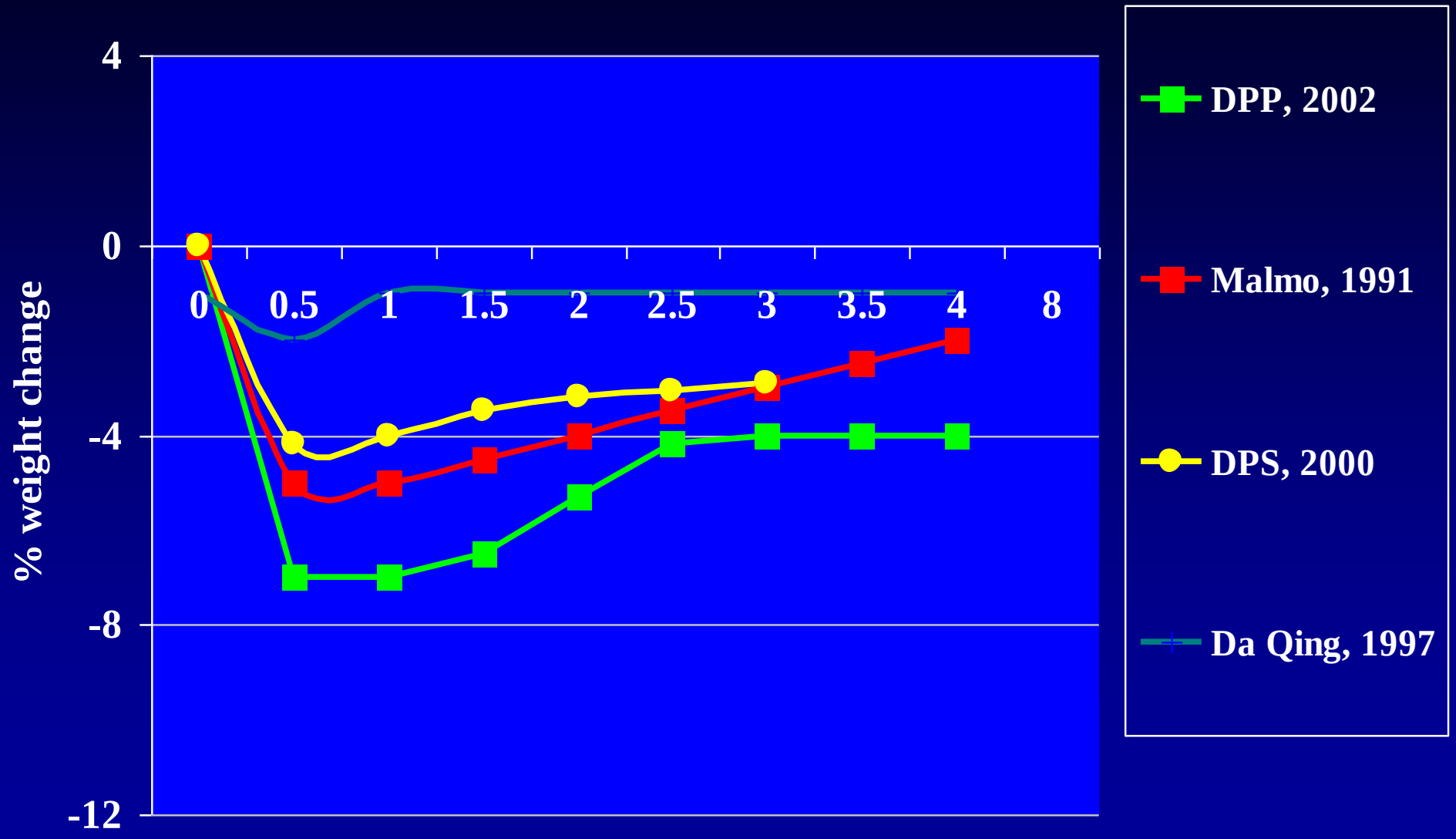
T2D risk was reduced when any of the pre-specified lifestyle target was achieved- DPS

TARGET	ALL PARTICIPANTS OR	(95% CI)
Weight loss >5%	0.34	(0.12-0.50)
Total Fat < 30E%	0.47	(0.28-0.81)
Saturated Fat < 10 E%	0.46	(0.16-0.81)
Fiber > 15 g/1000 kcal	0.29	(0.12-0.69)
Exercise >4h/week	0.38	(0.23-0.64)

RR for diabetes according to weight change from baseline to year 1:
DPS - Combined group



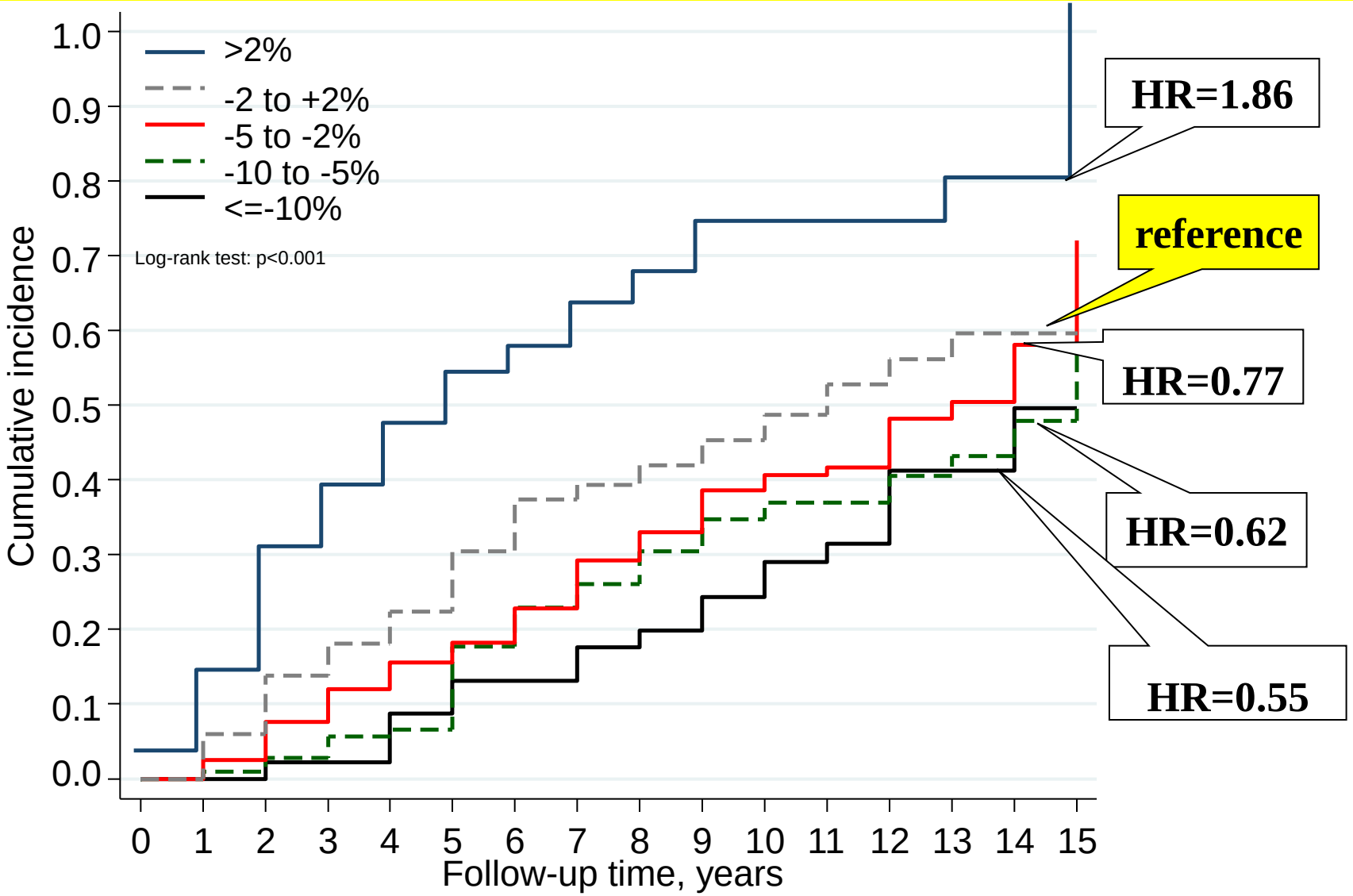
Net Weight Loss (%) of Long-term, Lifestyle-based, Weight Loss Interventions Evaluating Primary Prevention of Diabetes



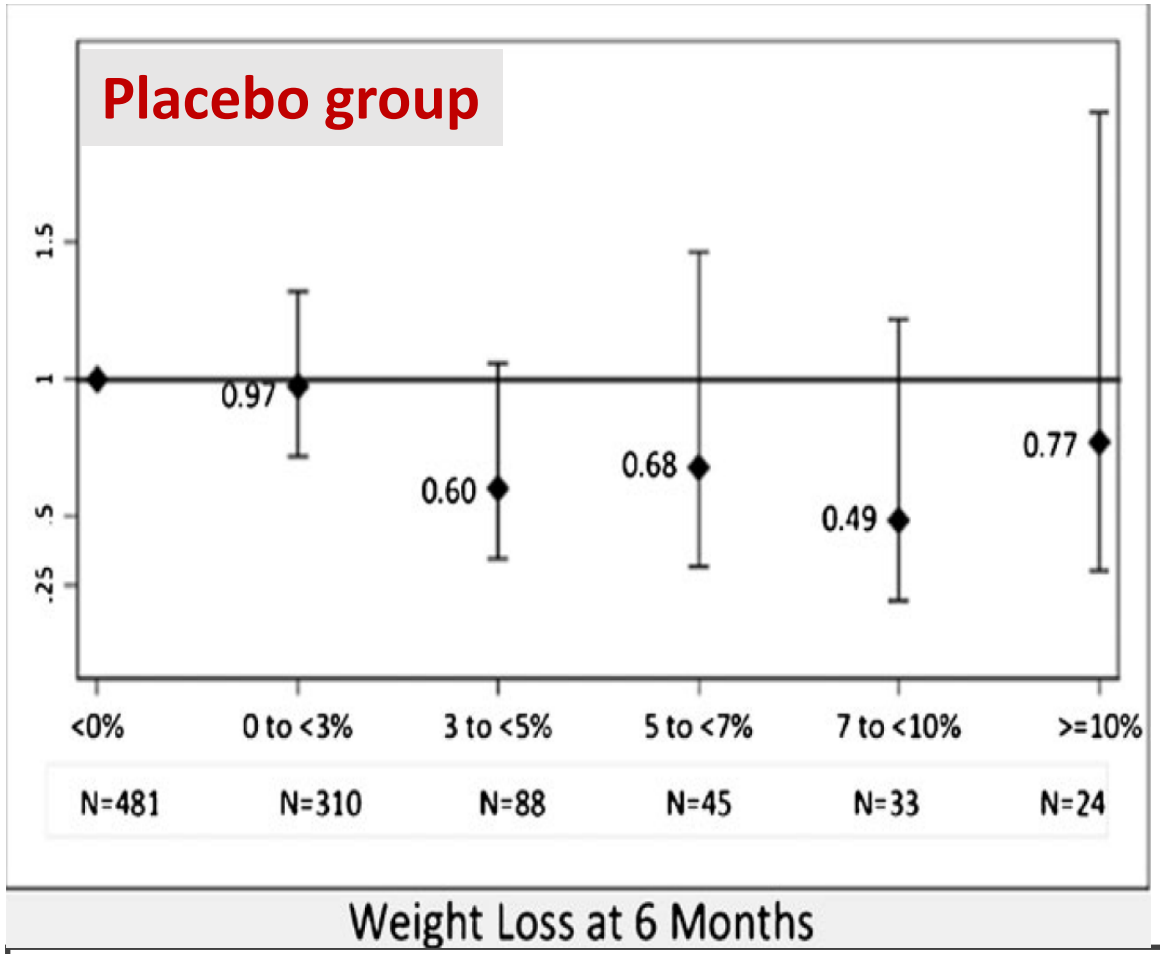
DPS: prevention is predicted by weight change at year 1

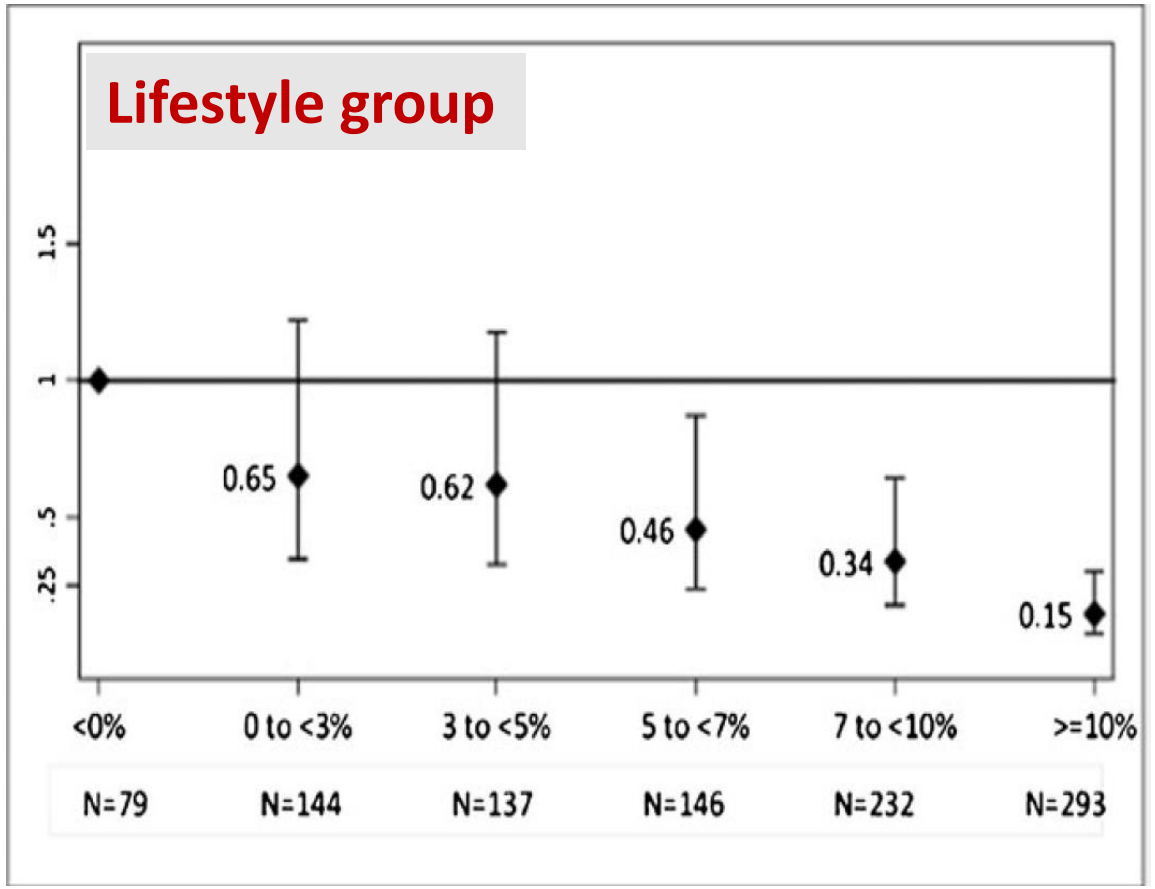
1 kg weight reduction at year 1 → 7% risk reduction

(adjusted for sex, baseline age, 2h glucose, BMI)



DPS follow-up until 2009





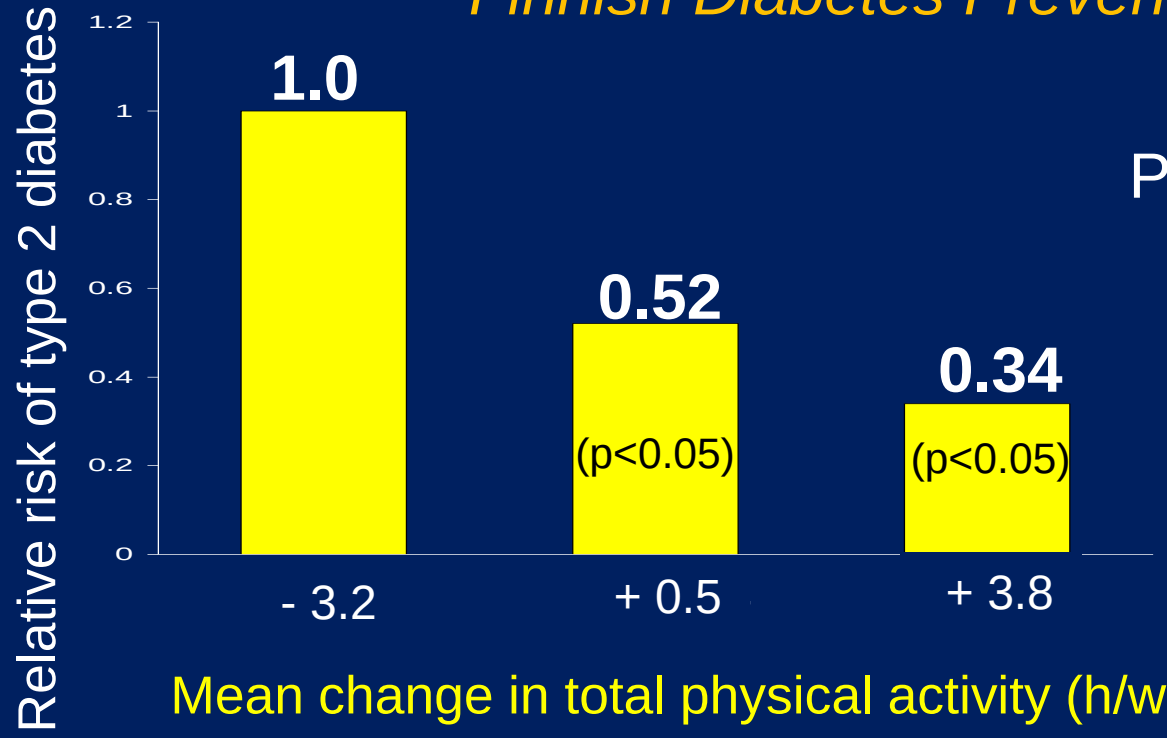
Weight Loss at 6 Months

Early Response to Preventive Strategies in the US Diabetes Prevention Program

Maruthur N, et al. J Gen Intern Med 2013;28:1629–36

Total physical activity prevented type 2 diabetes in high-risk individuals*

Finnish Diabetes Prevention Study (DPS)



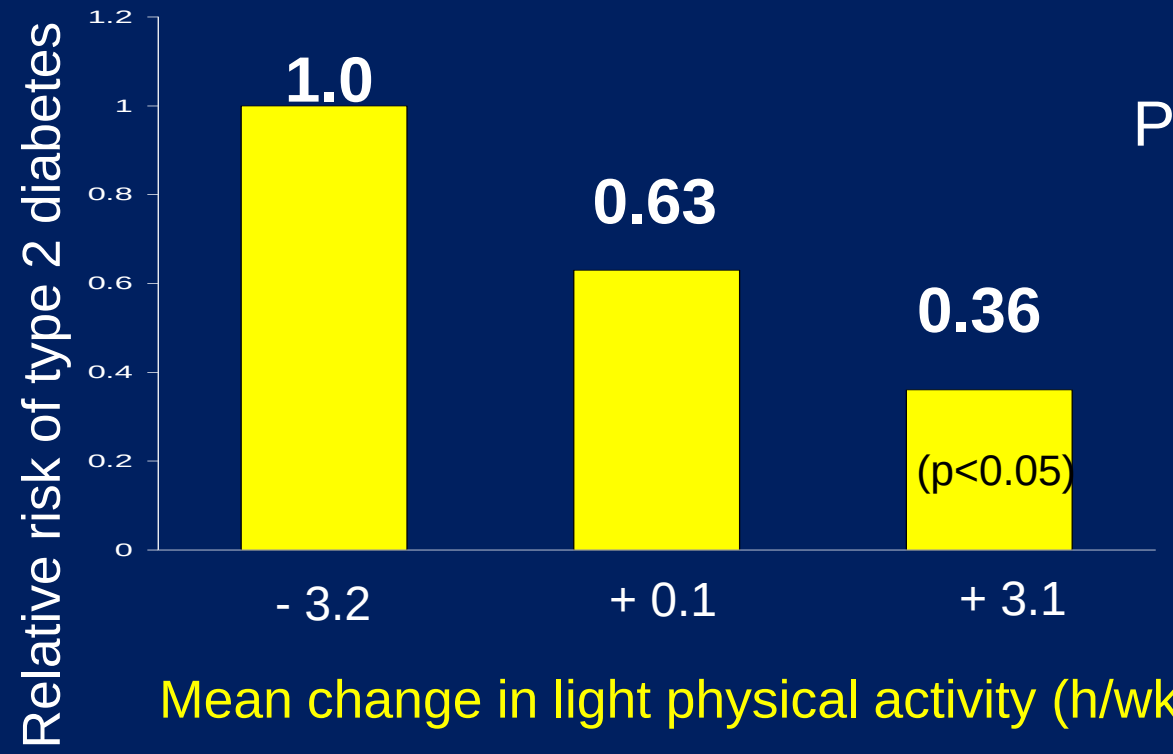
P < 0.001 for linear trend

*** Adjusted for all baseline and during-study variables**

Laaksonen DE et al. Diabetes 2005

Light physical activity (<3.5 METs) prevented type 2 diabetes in high-risk individuals *

Finnish Diabetes Prevention Study (DPS)

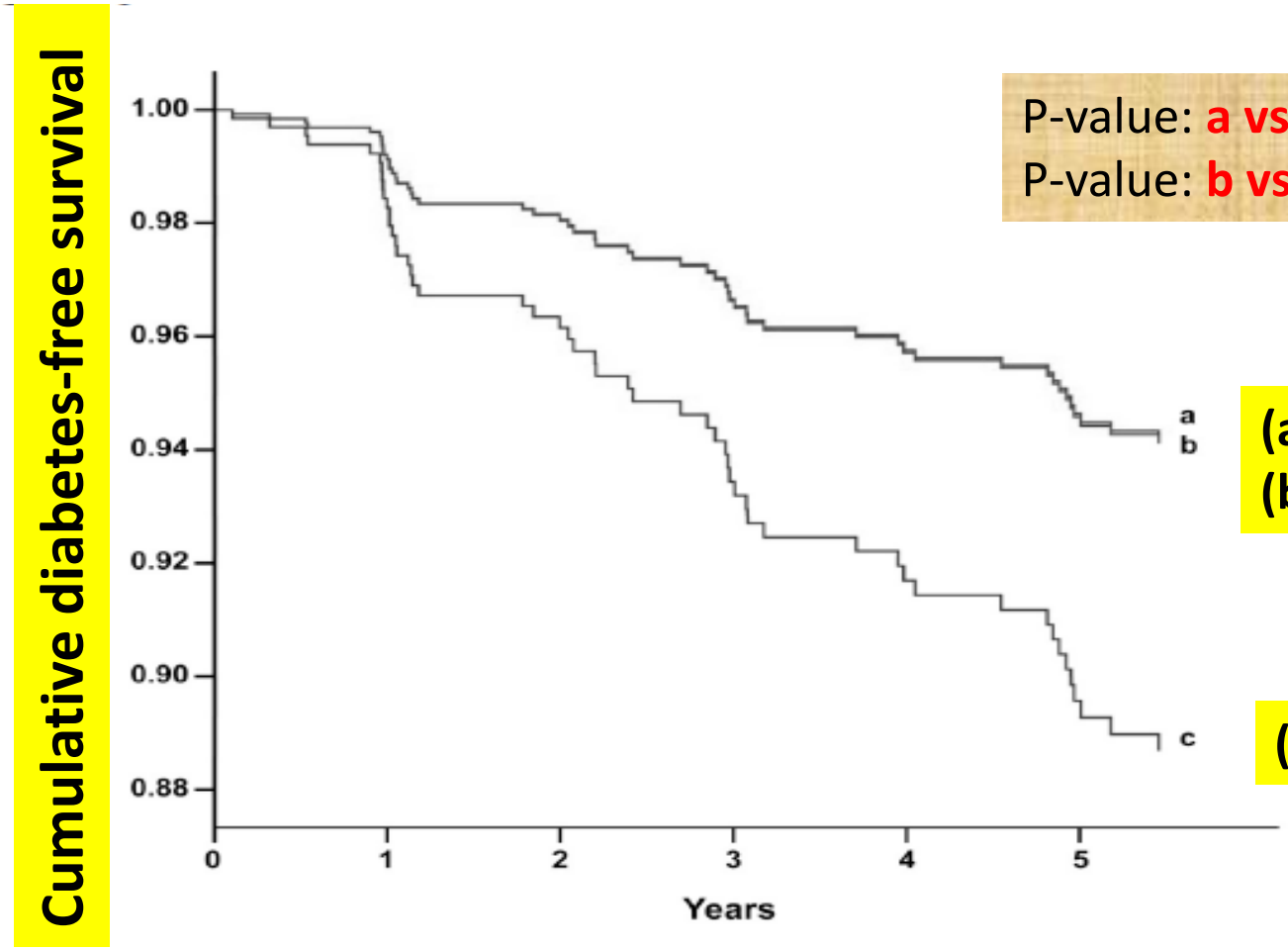


P = 0.001 for linear trend

*** Adjusted for all baseline and during-study variables**

Laaksonen DE et al. Diabetes 2005

Reduction in the Incidence of Type 2 Diabetes with the Mediterranean Diet: The PREDIMED-Reus Nutrition Intervention Randomized Trial



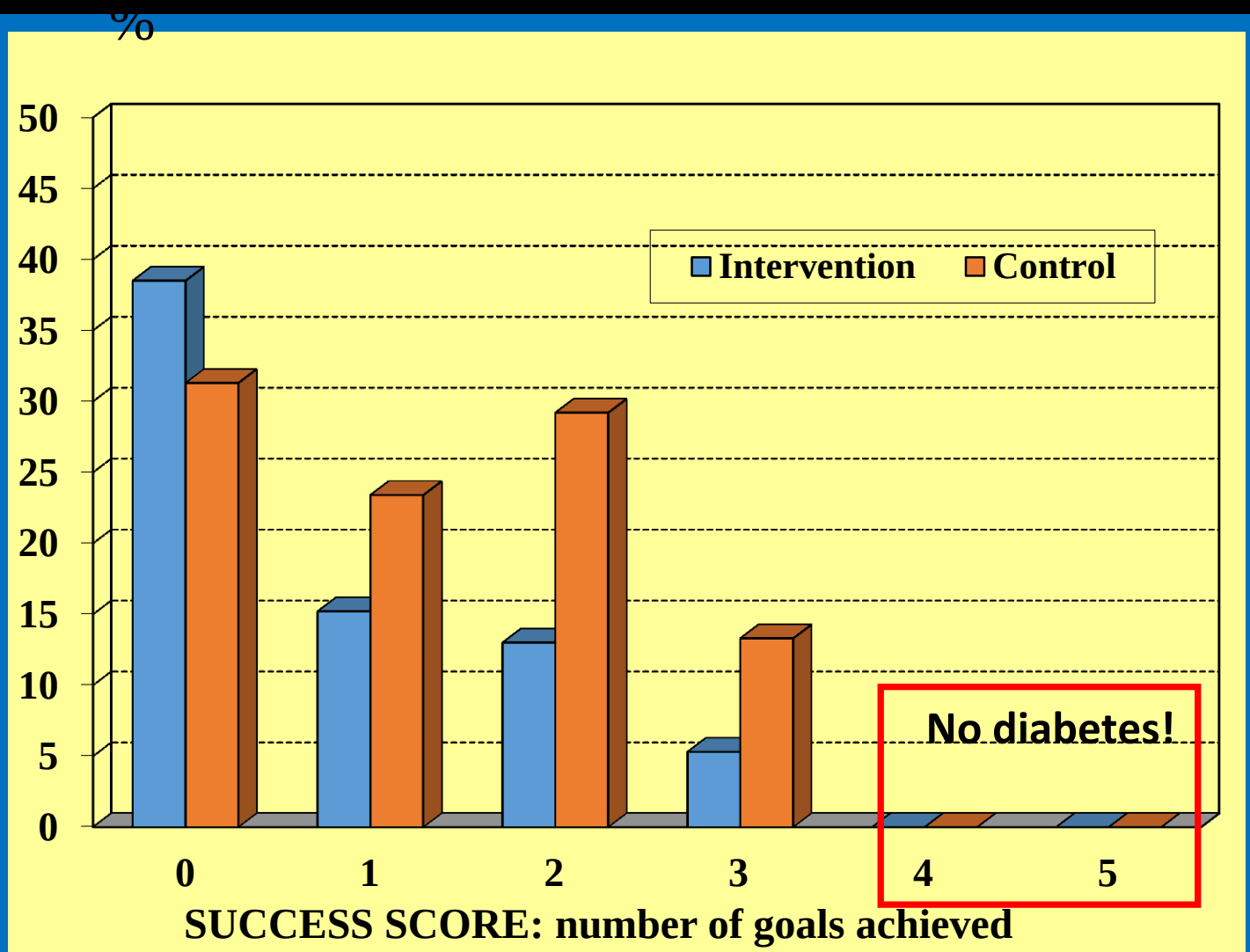
P-value: **a vs. c** = 0.047
P-value: **b vs. c** = 0.053

(a) MedDiet + Extra Virgin olive oil
(b) MedDiet + Nuts

(c) Control diet

Salas-Salvadó J et al. Diabetes Care 2011;34:14-9.

The best tool to avoid the progression from IGT to T2D: Multimodal intervention! - DPS

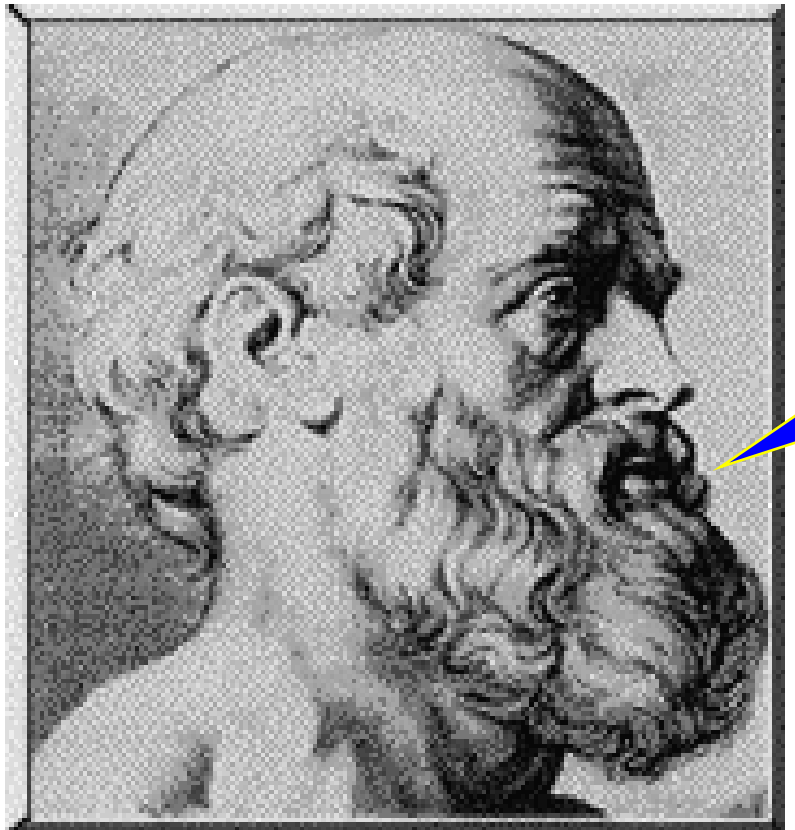


Intervention goals:

- Weight reduction > 5%
- Fat intake < 30 E%
- Saturated fat intake < 10 E%
- Fibre intake/1000kcal ≥ 15 g
- Physical activity/day > 30 min

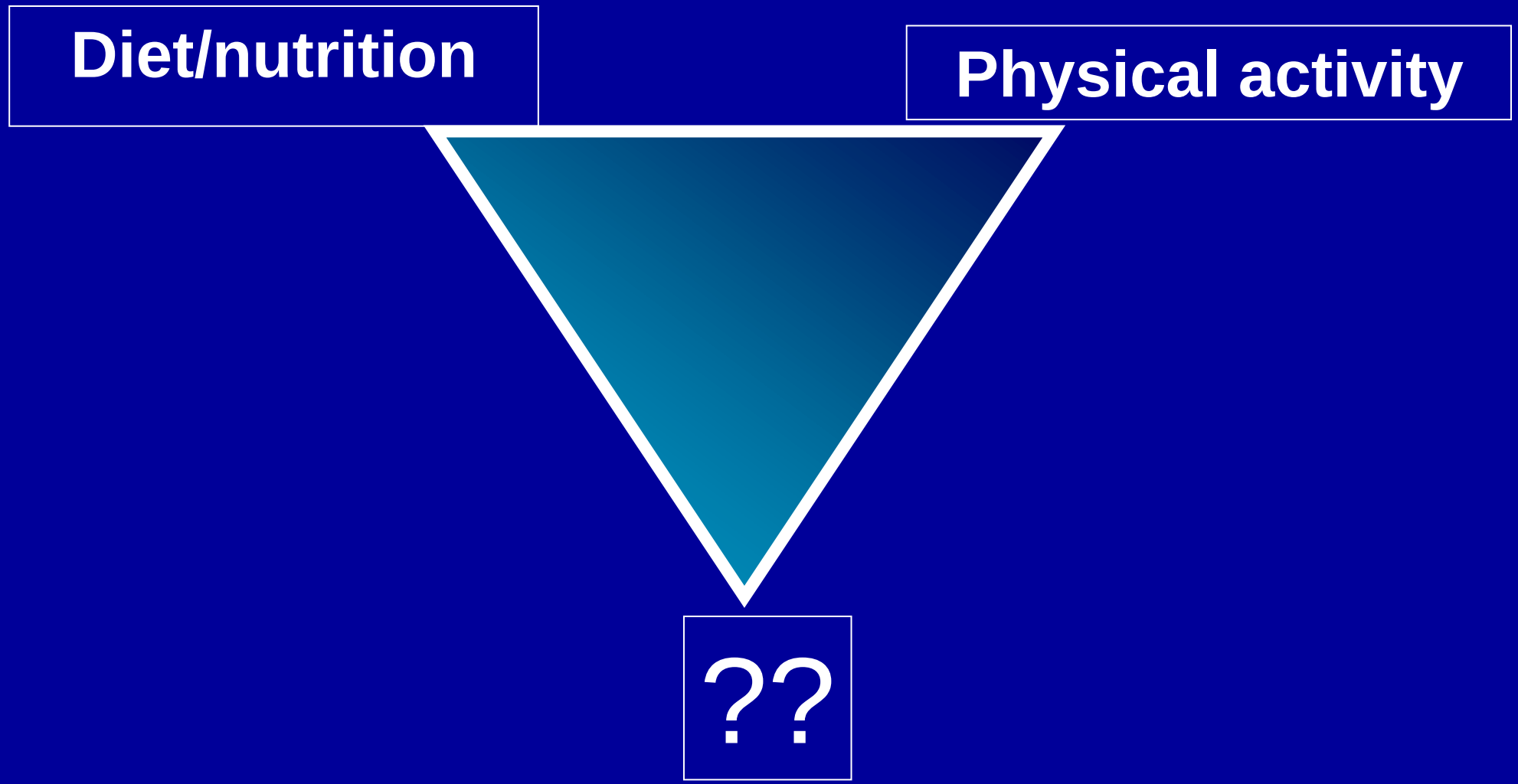
Multimodal

Hippocrates
Father of Medicine
(460 - 377 BC)

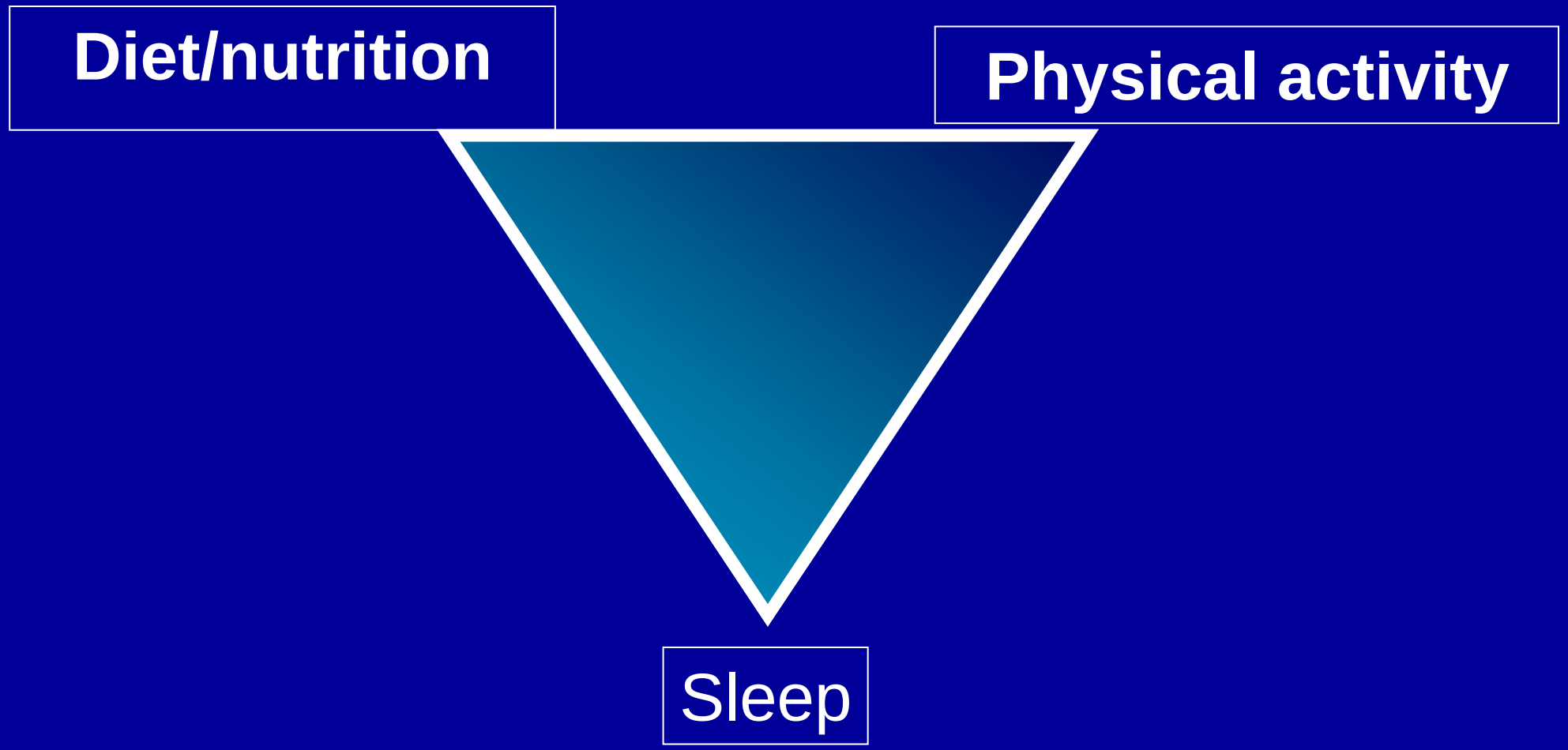


"Eating alone will not keep a man well.
He must also take exercise.
For food and exercise,
while possessing opposite qualities,
yet work together to produce health."

3 pillars of lifestyle

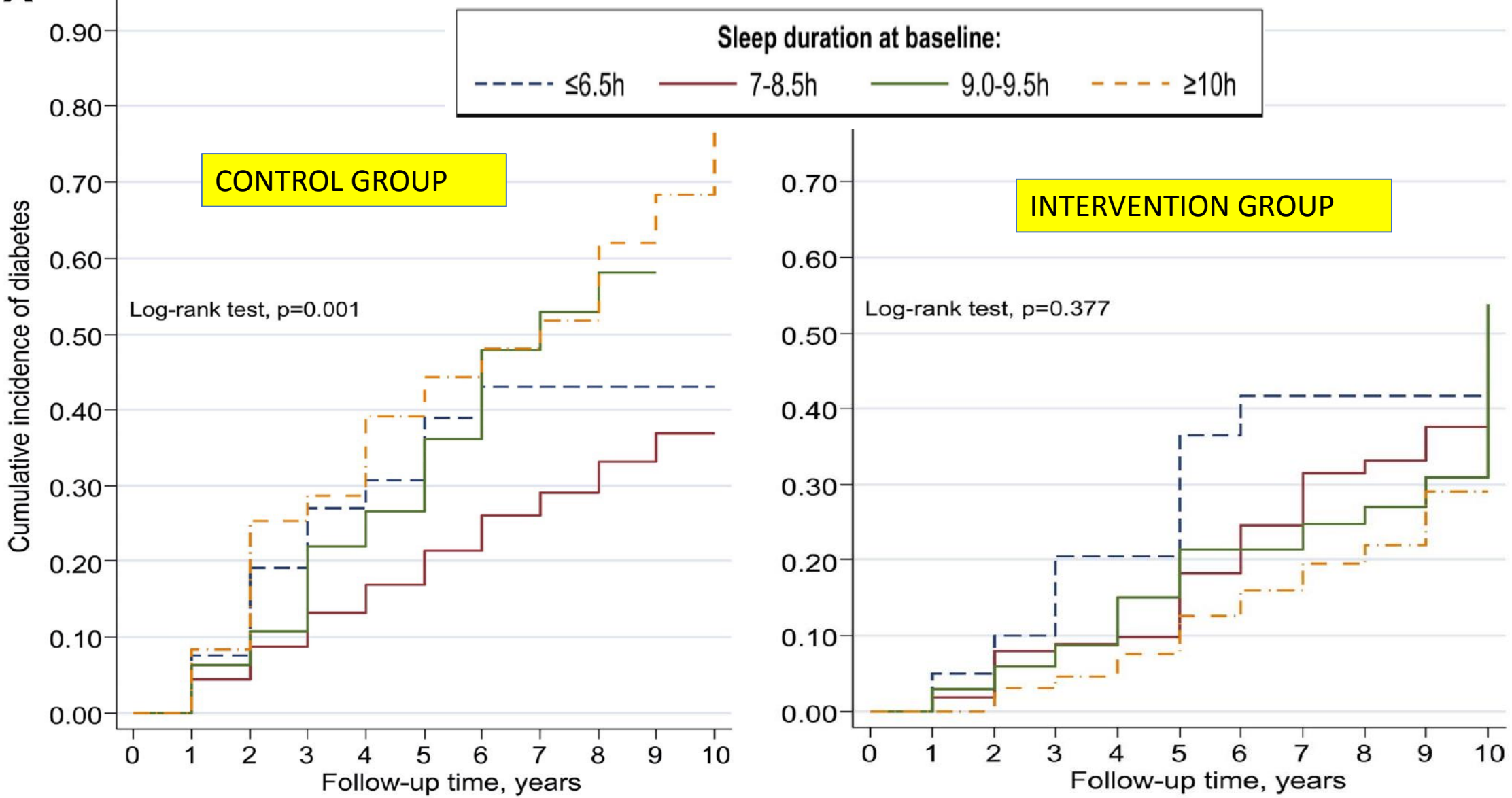


3 pillars of lifestyle



SUB-GROUP ANALYSIS/ POST-HOC ANALYSIS

- Try to explore where the trial effect came from
- Who benefitted most?
- Who did not benefit?
- Problematic, when the primary end point not significant – chance findings
- Some scientists argue that this should never done
- Can be defined in the original statistical analysis plan



SLEEP DURATION AND THE PROGRESSION TO DIABETES - DPS

Tuomilehto H et al. Diabetes Care 2009;32:1965

Can changes in physical activity patterns be maintained for older age?

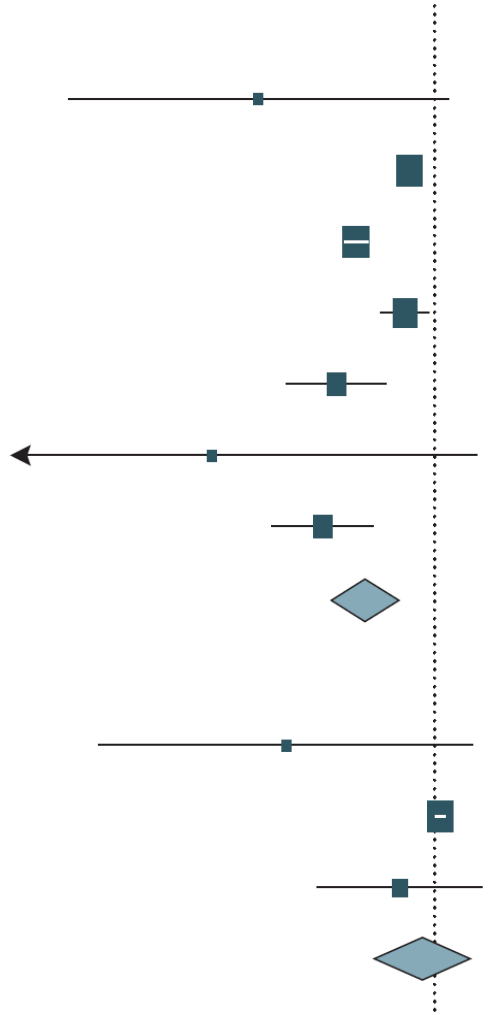
YES: ...

Relative risk of diabetes by age – DPS
Older people benefitted more.

Age tertile (years)	Relative Risk Reduction
< 51	49 %
51 - 60	57 %
61 -	65 %

Relative Risks (RRs) and Diabetes Incidence Rates Among medication Studies Stratified by Drug Class

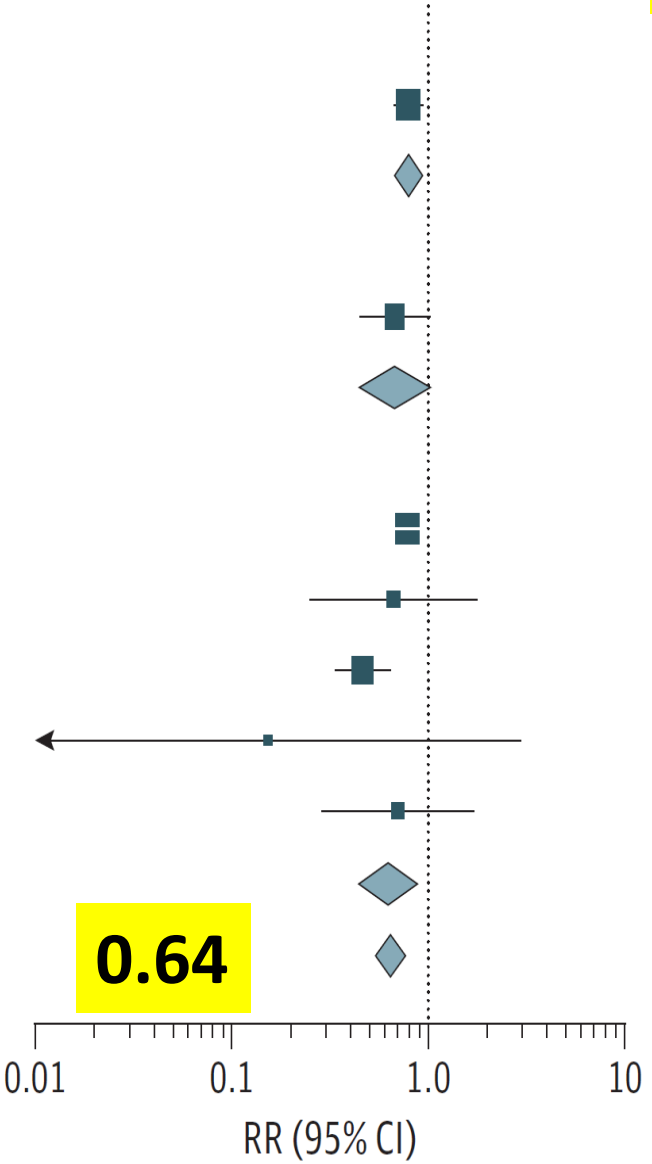
Insulin sensitizers						
Li et al,[61] 1999	Metformin	3.00	18.0	1.0	6	0.15 (0.02-1.17)
DPP,[33] 2002	Metformin	7.80	11.0	236.0	313	0.76 (0.66-0.88)
DREAM,[72] 2006	Rosiglitazone	4.00	8.0	280.0	658	0.43 (0.37-0.48)
IDPP,[44] 2006	Metformin	16.00	22.0	51.0	73	0.73 (0.56-0.94)
CANOE,[62] 2010	Metformin plus rosiglitazone	3.00	10.0	14.0	41	0.34 (0.20-0.59)
Lu et al,[63] 2011	Metformin	0.50	6.1	0.5	5	0.09 (0.01-1.58)
ACT NOW,[64] 2011	Pioglitazone	2.10	7.6	15.0	50	0.30 (0.17-0.52)
Subgroup RR						0.47 (0.32-0.68)
Insulin secretagogues						
Eriksson et al,[65] 2006	Glipizide	4.0	20.0	1.0	5	0.20 (0.03-1.53)
NAVIGATOR,[73] 2010	Nateglinide	7.2	6.8	1674.0	1580	1.06 (1.01-1.12)
DIANA,[66] 2012	Nateglinide	12.0	17.0	7.0	10	0.69 (0.28-1.68)
Subgroup RR						0.87 (0.52-1.46)



Haw S, et al. JAMA Intern Med 2017

Relative Risks (RRs) and Diabetes Incidence Rates Among medication Studies Stratified by Drug Class

Insulin						
ORIGIN,[67] 2012	Insulin glargine	2.0	3.0	182.0	224	0.79 (0.67-0.94)
Subgroup RR						0.79 (0.67-0.94)
Hormone therapy						
HERS,[68] 2003	Estrogen/progestin	6.0	9.0	24.0	46	0.68 (0.45-1.02)
Subgroup RR						0.68 (0.45-1.02)
Alpha-glucosidase inhibitors						
STOP-NIDDM,[69] 2002	Acarbose	10.0	13	221.0	285	0.78 (0.68-0.90)
DAISI,[70] 2008	Acarbose	6.0	8.0	5.0	9	0.67 (0.25-1.78)
Kawamori et al,[71] 2009	Voglibose	2.0	4.0	50.0	106	0.46 (0.34-0.64)
Lu et al,[63] 2011[a]	Acarbose	0.3	4.7	0.5	3	0.15 (0.01-2.97)
DIANA,[66] 2012[a]	Voglibose	12.0	17.0	7.0	10	0.70 (0.29-1.71)
Subgroup RR						0.62 (0.44-0.88)
Overall RR						0.64 (0.54-0.76)



Haw S, et al. JAMA Intern Med 2017

Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES)

John P Armato, Ralph A DeFronzo, Muhammad Abdul-Ghani, Ron J Ruby

***Lancet Diabetes Endocrinol* 2018**

Published **Online**

September 14, 2018

422 stratified

Methods We did a retrospective observational study of people at increased risk of type 2 diabetes from a community practice in southern California, USA. Participants had an oral glucose tolerance test and were assigned a risk stratification on the basis of presence and severity of insulin resistance, impaired β-cell function, and glycaemia

200 assigned lifestyle modification
51 received less than 1 year of treatment

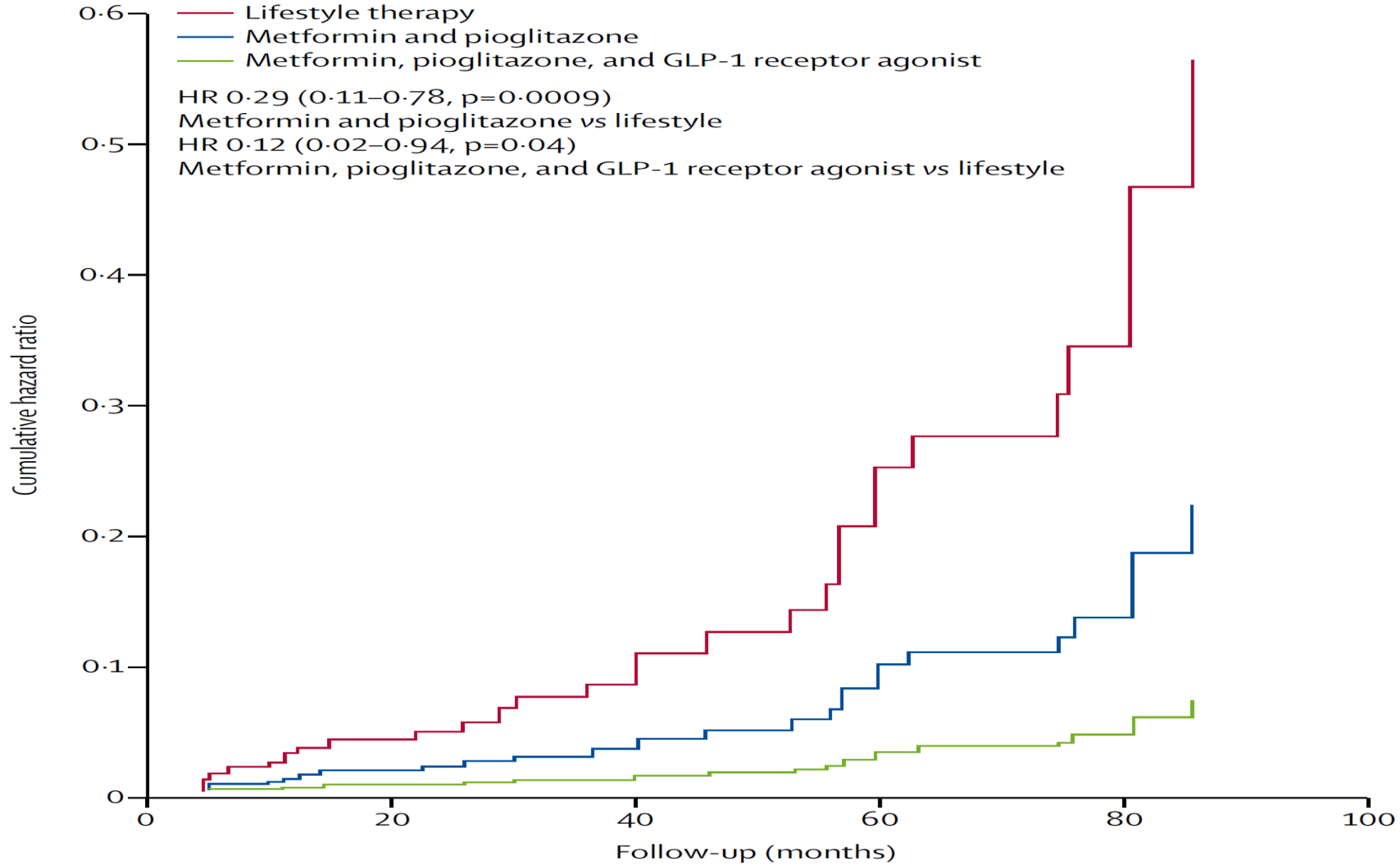
Drop-out 26%

141 assigned pioglitazone and metformin
35 received less than 1 year of treatment

Drop-out 26%

81 assigned pioglitazone, metformin, and GLP-1 receptor agonist
27 received less than 1 year of treatment

Drop-out 33%



Lifestyle therapy	200	117	61	30	12
Metformin and pioglitazone	141	90	52	31	12
Metformin, pioglitazone, and GLP-1 receptor agonist	81	40	24	12	3

NON-COMPLIANCE

- Non-compliance decreases the statistical power of the trial which speaks about the validity (truth of the results)
- Extent of non-compliance is directly proportional to the duration and complexity of the trial.
- Compliance is difficult when the end –points are time taking like incidence of cancers or death

Table. Random Effects Meta-analyses Exploring RR for Diabetes Among LSM and Medication Studies After Treatment Withdrawal

JAMA Intern Med. doi:10.1001/jamainternmed.2017.6040
Published online November 6, 2017.

Medication Trials				Follow-up[a]	End of Follow-up, RR (95% CI)
Eriksson et al,[65] 2006	Glipizide	0.5	0.41 (0.01-11.3)	52 wk	0.20 (0.03-1.53)
DREAM,[22,72] 2006, 2011	Rosiglitazone	3.0	0.43 (0.37-0.48)	10 wk	1.07 (0.88-1.32)
DREAM,[22,57] 2006, 2011[b]	Ramipril	3.0	0.93 (0.82-1.04)	10 wk	1.08 (0.89-1.33)
DPP,[21,33] 2002, 2003	Metformin	2.8	0.76 (0.66-0.88)	2 wk	0.76 (0.68-0.85)
STOP-NIDDM,[69] 2002	Acarbose	3.0	0.78 (0.68-0.90)	12 wk	1.46 (0.90-2.36)
ORIGIN,[67] 2012	Insulin glargine	6.2	0.79 (0.67-0.94)	14 wk	0.86 (0.74-0.99)
Pooled estimate			0.71 (0.55-0.92)		0.95 (0.79-1.14)

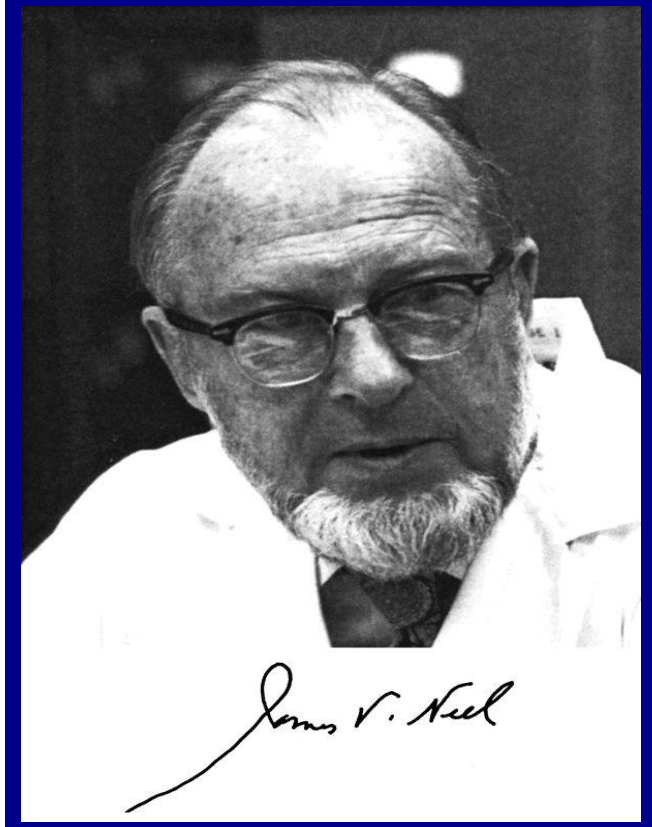
James V. Neel

Am J Hum Genet. **1962;14:363–375.**

Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"?

JAMES V. NEEL
Department of Human Genetics,
University of Michigan Medical School,
Ann Arbor, Mich.

FOR THE POPULATION GENETICIST, diabetes mellitus has long presented an enigma. Here is a relatively frequent disease, often interfering with reproduction by virtue of an onset during the reproductive or even pre-reproductive years, with a well-defined genetic basis, perhaps as simple in many families as a single recessive or incompletely recessive gene (cf. Allan, 1933; Pincus and White, 1933, 1934; Harris, 1950; Steinberg and Wilder, 1952; Lamy, Frézal and de Grouchy, 1957; Steinberg, 1959; Post, 1962a). If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic selection



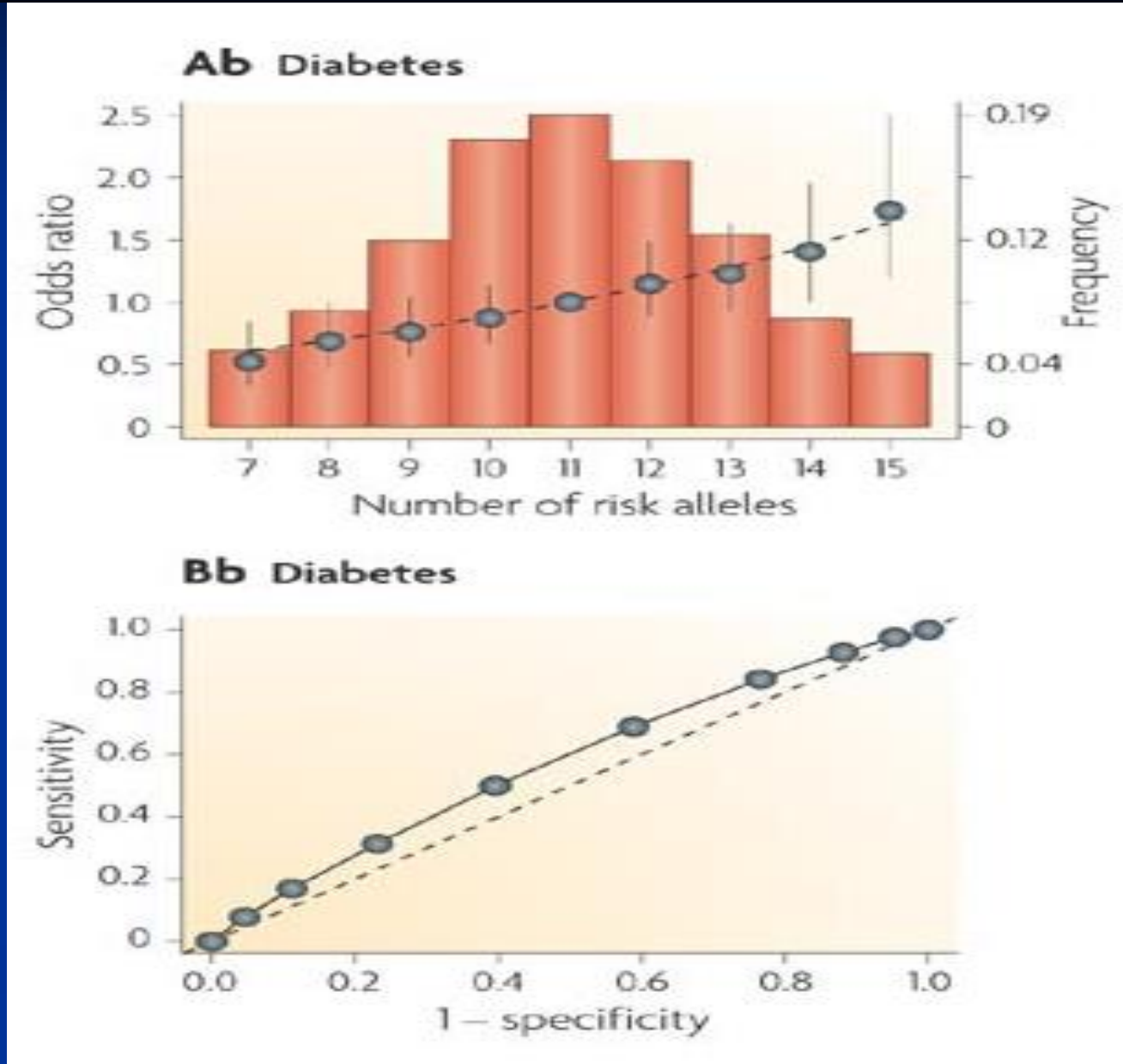
Interactions of genes and lifestyle in the prevention of T2D

How old is the link between overnutrition and diabetes?

- **Shared by humans, monkeys, rats, mice, dogs, monkeys, etc.**
- **Therefore over 100 million years old**

T2D susceptibility genes: Prediction of T2D

- Statistically significant association between multi-locus genetic score and T2D.
- <u>Not</u> effective in distinguishing future cases from non-cases.



Kraft P et al. Nature Reviews Genetics 2009

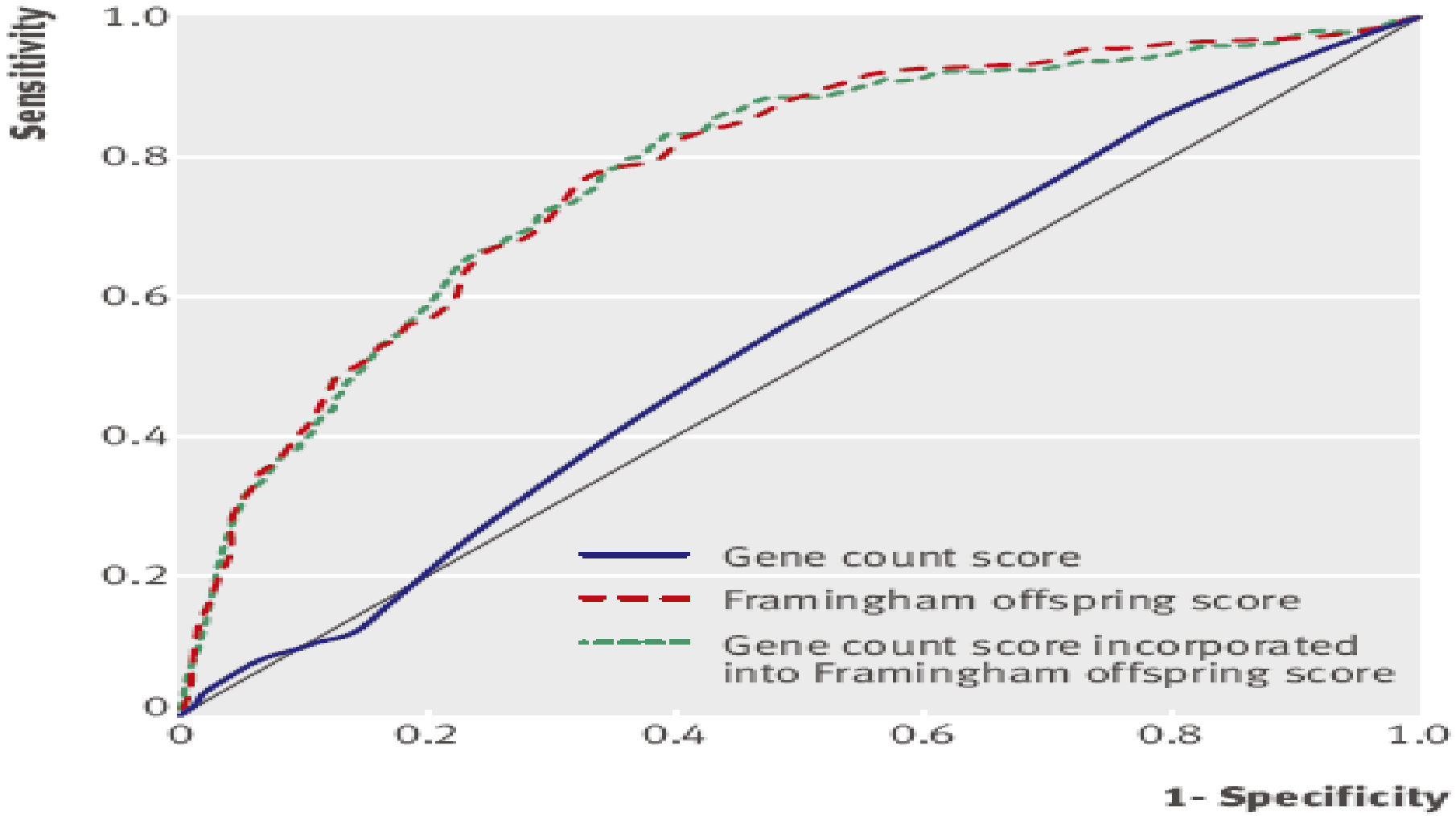
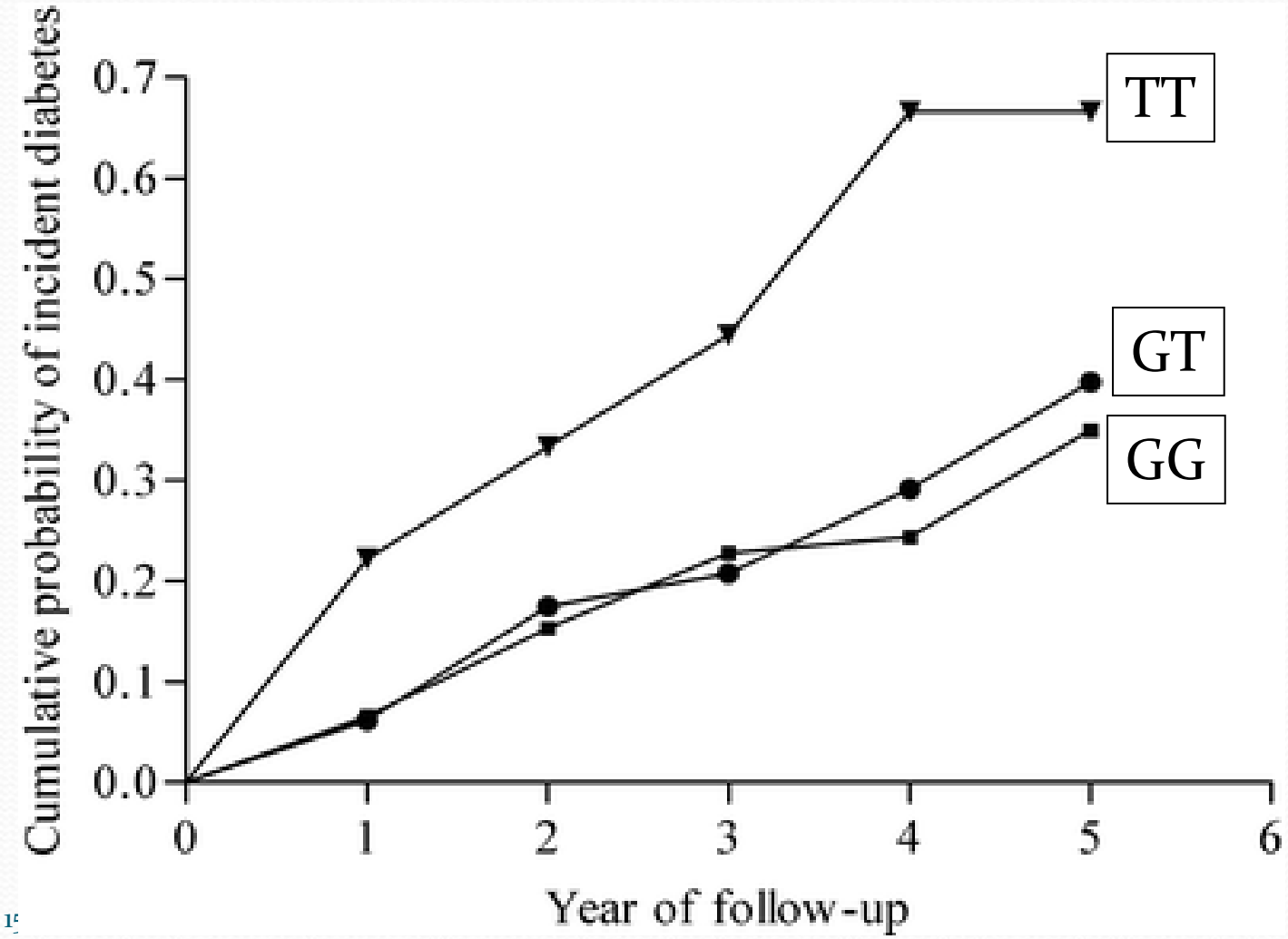


Fig 1 | Receiver operating characteristics curves for gene count score alone (area under curve 0.54, 95% CI 0.50 to 0.58), Framingham offspring risk score (area under curve 0.78, 0.75 to 0.82), and gene count score incorporated into Framingham offspring risk score (area under curve 0.78, 0.75 to 0.81)

Talmud et al. BMJ 2010;340:b4838

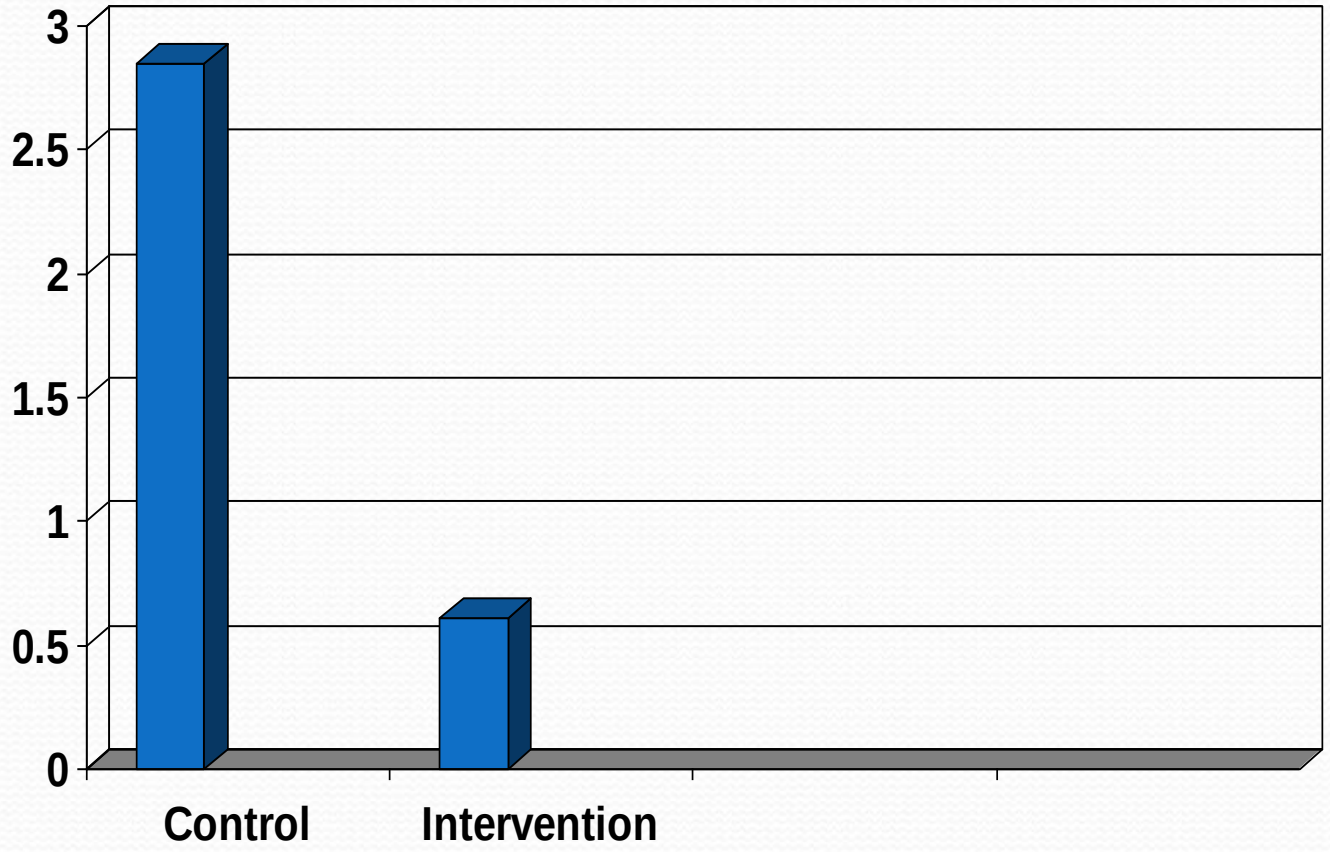
4-year probability of incident T2DM by *TCF7L2* rs 12255372 genotype – DPS control group



P=0.009

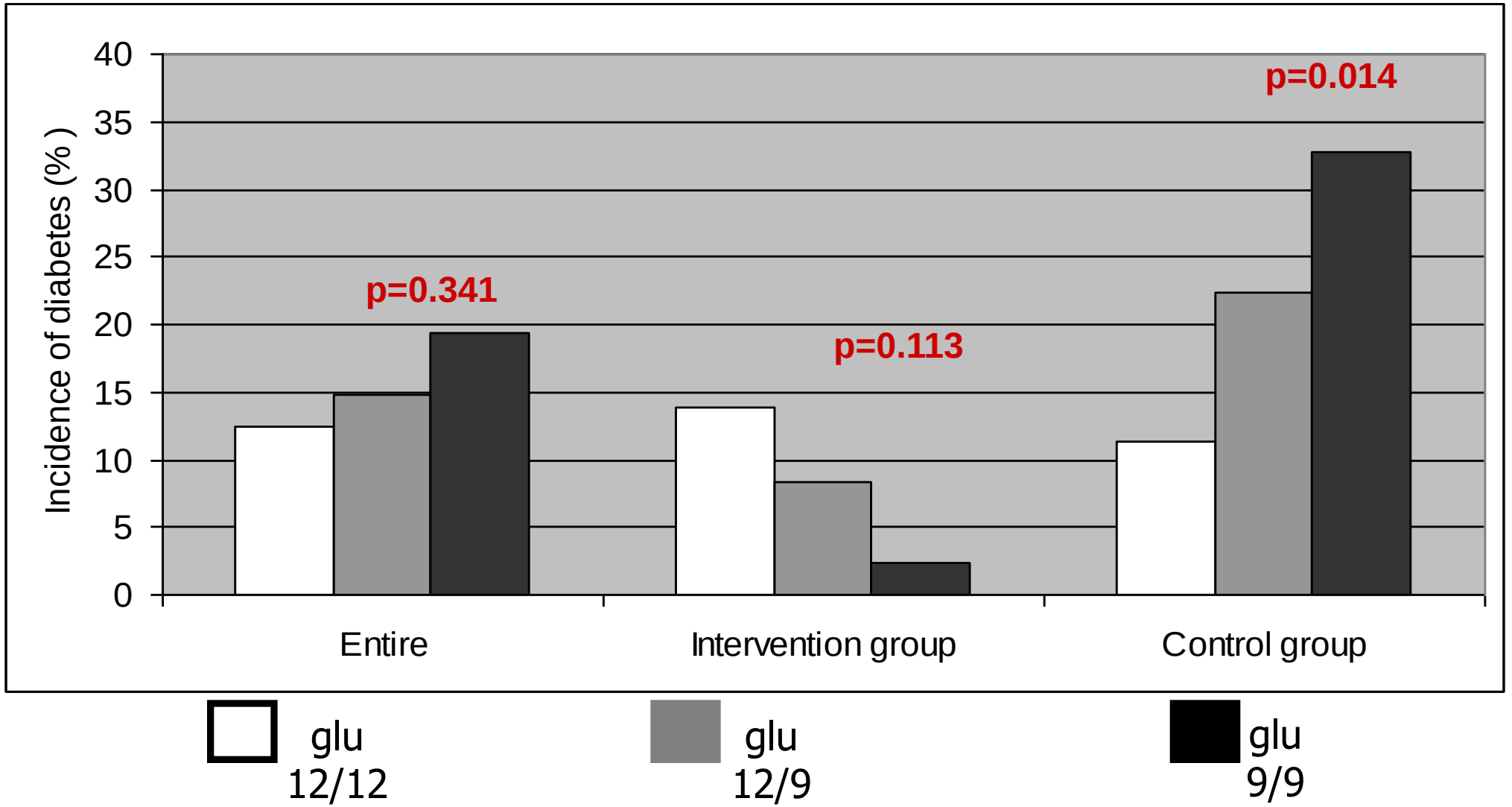
Wang et al. Diabetologia 2007

Gene-lifestyle interaction among people with *TCF7L2*-TT genotype (rs 12255372) - DPS

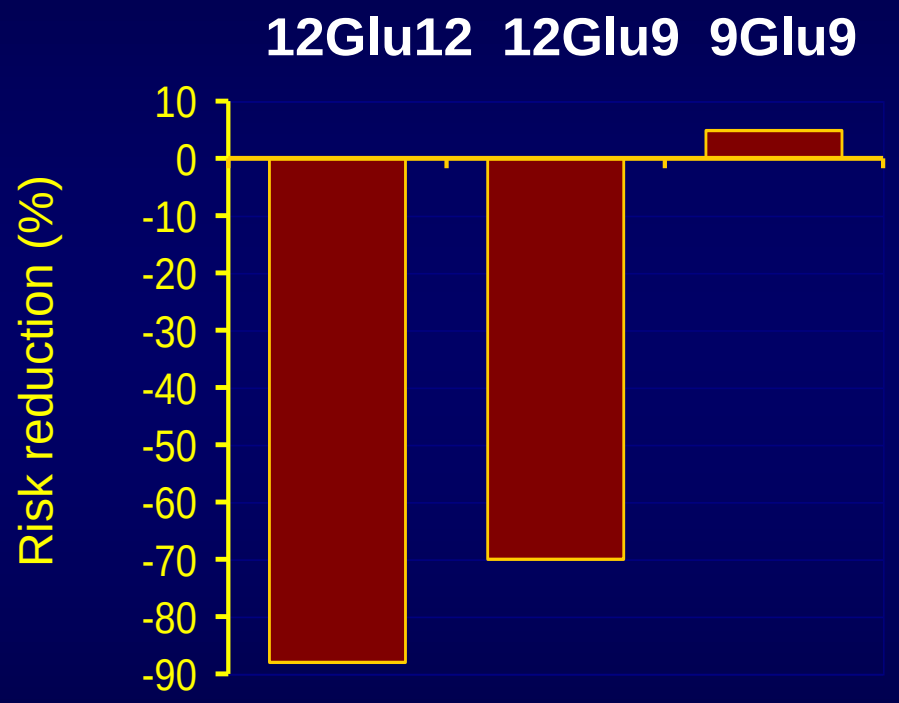


Wang et al. Diabetologia 2007

Incidence of type 2 diabetes by group according to α2B adrenergic receptor gene polymorphism -DPS



Finnish DPS – Effect modification by the 12Glu9 polymorphism of the α2B adrenergic receptor gene on lifestyle changes

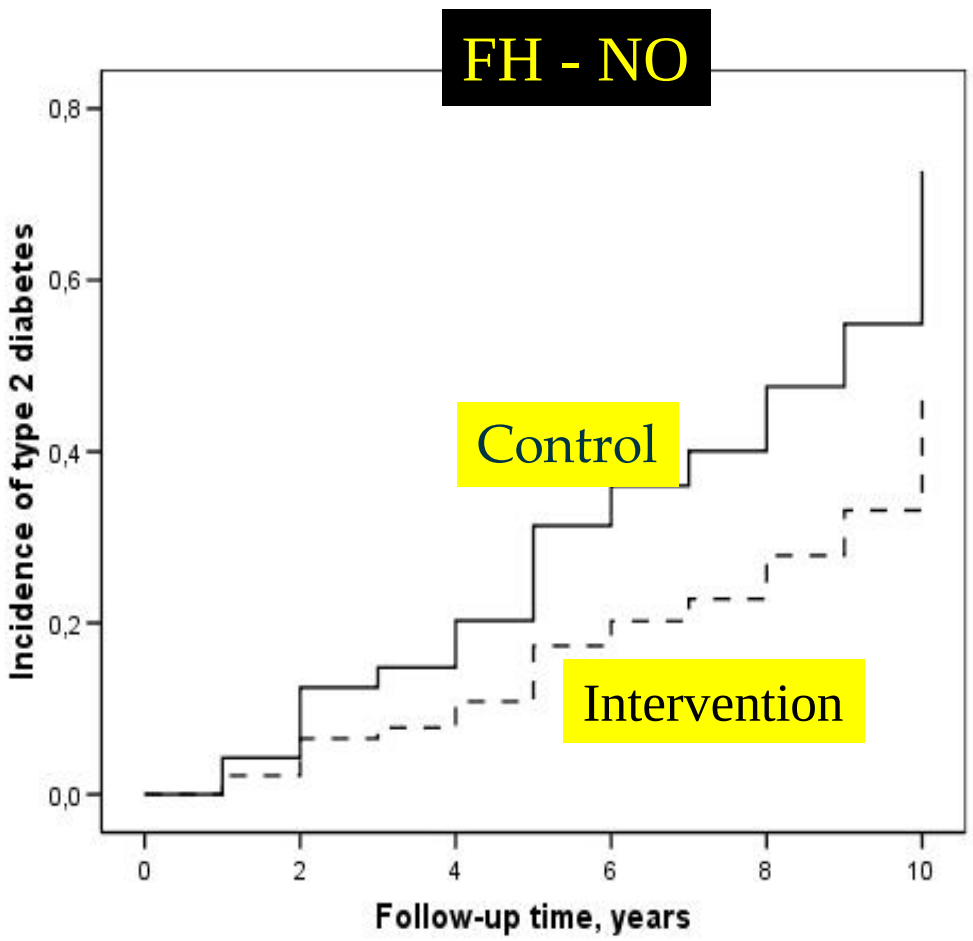


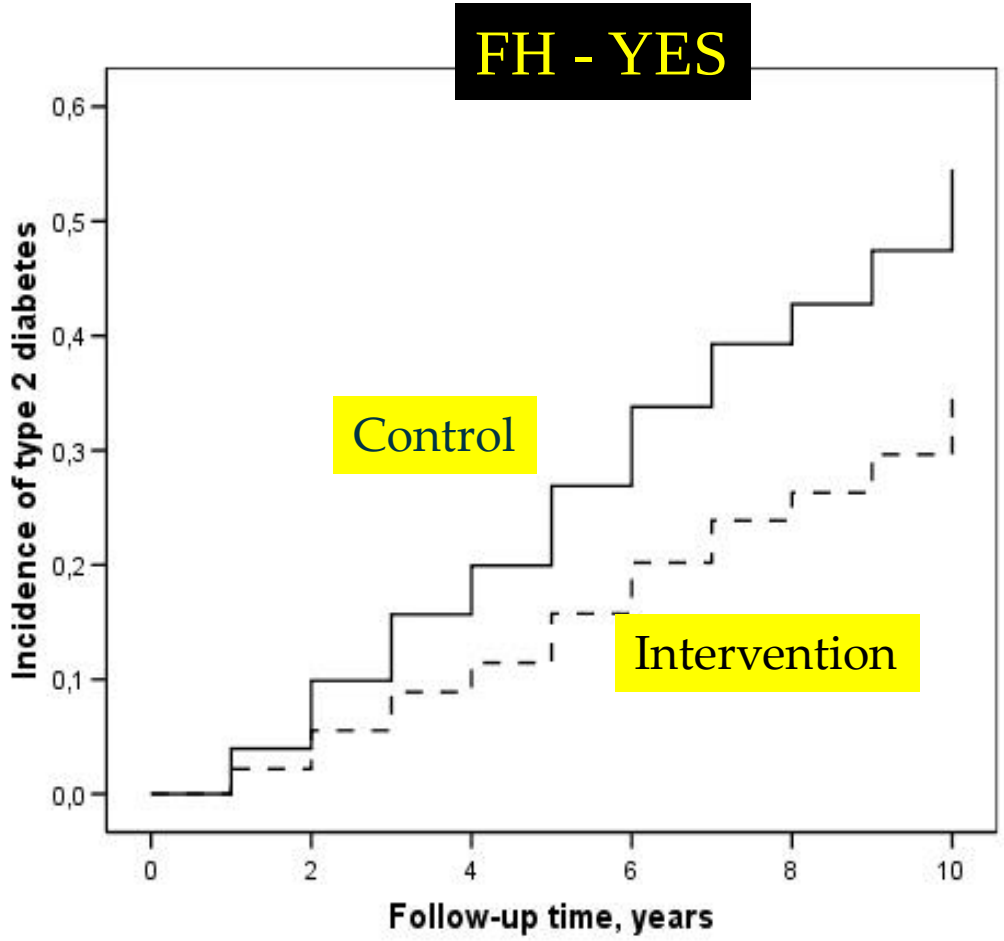
Change in **total LTPA**, upper vs. lower third

Change in **dietary score**, upper vs. lower third

Laaksonen et al. 2007

DPS: Incidence of diabetes according to the Family History (FH) of diabetes





Uusitupa, et al. Diabetes Care 2011