Improved lifestyle and decreased diabetes risk over 13 years: The Finnish Experience
Matti Uusitupa, Public Health and Clinical Nutrition, University of Eastern Finland
Content of the presentation

• Main risk factors of Type 2 diabetes (T2DM)
• Summary results from the Finnish Diabetes Prevention Study (DPS)
• Impact of genes, family history vs. lifestyles
• Post intervention results
• Practical implementations for prevention based on the Finnish experience
• Conclusions
The number of adults (20-79 years) with diabetes has tripled during the last 2 decades, millions

IDF: Diabetes Atlas 2017
Type 2 diabetes risk factors

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

Modifiable risk factors
- Overweight / obesity
- Abdominal obesity
- Low physical activity
- Smoking
- Unhealthy diet

Possibly modifiable risk factors
- Sleep deprivation
- Distress and depression
- Persistent organic pollutants (e.g. pesticides, solvents, pharmaceuticals)
- Microbiota
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>N</th>
<th>Drop-out rate</th>
<th>FU time</th>
<th>Risk reduction</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Da-Qing Study China</td>
<td>Diet Exercise Diet+exercise Control</td>
<td>130 141 126 133</td>
<td>8%</td>
<td>6 years</td>
<td>31% 46% 42%</td>
<td>Pan et al. 1997. Diabetes Care 20:537-544</td>
</tr>
<tr>
<td>The DPS Finland</td>
<td>Diet+physical activity Control</td>
<td>265 257</td>
<td>8%</td>
<td>3,2 years</td>
<td>58%</td>
<td>Tuomilehto et al 2001. new Engl J Med</td>
</tr>
<tr>
<td>The DPP USA</td>
<td>Diet+physical activity Metformin Placebo</td>
<td>1079 1073 1082</td>
<td>8%</td>
<td>2,8 years</td>
<td>58% 31%</td>
<td>DPP research group 2002. New Engl J Med 346:393-403</td>
</tr>
<tr>
<td>IDDP India</td>
<td>Lifestyle Metformin Lifestyle+metformin Control</td>
<td>133 133 129 136</td>
<td>5%</td>
<td>30 months</td>
<td>28,5% 26,4% 28,2%</td>
<td>Ramachandran et al. 2006. Diabetologia 49:289-97</td>
</tr>
<tr>
<td>The SLIM Study The Netherlands</td>
<td>Diet+physical activity Control</td>
<td>74 73</td>
<td>8%</td>
<td>3 years</td>
<td>58%</td>
<td>Roumen et al. 2008. Diabetic Medicine 25:597-605</td>
</tr>
<tr>
<td>EDIPS Newcastle UK</td>
<td>Diet+physical activity Control</td>
<td>51 51</td>
<td>19%</td>
<td>3,1 years</td>
<td>55%</td>
<td>Penn et al 2009. BMC Public Health 9</td>
</tr>
</tbody>
</table>
Finnish Diabetes Prevention Study (DPS)

• The first randomised controlled study to show that Type 2 diabetes is preventable by changing lifestyles
• Started in 1993 in Helsinki and Kuopio, other centres Turku, Tampere and Oulu
• Highly quoted
• Over 80 research papers published so far
• Partner in international GWAS and biomarker consortia
PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTROM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HAMALAINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKA KEINANEN-KUKKANENI, M.D., PH.D., MAURI LAASKO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study

Jaana Lindstrom, Pirjo Ilanne-Parikka, Marika Pelkonen, Silja Auranen, Johan G. Eriksson, Kari Heräla, Helena Hamalainen, Pirjo Hiltunen, Sirkka Keinanen-Kukkanen, Mauri Laasko, Anne Louheranta, Merja Rastas, Virpi Salminen, and Matti Uusitupa, on behalf of the Finnish Diabetes Prevention Study Group

Summary
Background Lifestyle interventions can prevent the deterioration of impaired glucose tolerance to manifest type 2 diabetes, at least as long as the intervention continues. In the extended follow-up of the Finnish Diabetes Prevention Study, we assessed the extent to which the originally achieved lifestyle changes and risk reduction remain after discontinuation of active counselling.
Development of diabetes during the lifestyle intervention in the intervention and control groups – DPS (Tuomilehto et al. NEJM 2001)

Risk reduction: 58 %
Genetics of Type 2 Diabetes

• Individual risk for T2DM is strongly influenced by genetic factors
• In aggregate, common genetic variants explain only a small fraction of disease
• No major role for low frequency variants, either (Locke A et al. Genetic architecture of Type 2 diabetes, Nature 2016)

• Interaction studies in the DPS: single gene polymorphisms and genetic risk score approach
4-year probability of incident T2DM by TCF7L2 rs 12255372 genotype – DPS control group

Wang et al. Diabetologia 2007

TT
GT
GG

P=0.009
Gene-diet interaction with regard to $TCF7L2$-TT genotype of rs 12255372 - **DPS**

Wang et al. Diabetologia 2007
Impact of Positive Family History and Genetic Risk Variants on the Incidence of Diabetes

The Finnish Diabetes Prevention Study

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Markku Peltonen, PhD5
Johan G. Eriksson, MD, PhD5,6,7,8
Jaana Lindström, PhD7
Sirkka Aunola, PhD9

Pirjo Ilanne-Parikka, MD10,11
Sirkka Keinanen-Kiukkaanniemi, MD, PhD12,13
Jaakko Tuomilehto, MD, PhD4,5,14
Markku Laakso, MD, PhD3

Both genetic and environmental factors play major roles in the development of type 2 diabetes mellitus. In recent years, the research aiming to explore the genetic basis of type 2 diabetes has progressed significantly. Currently, >30 genetic variants have been identified...
Benefits of lifestyle prevention of diabetes according to the Family History (FH) of diabetes - DPS

Uusitupa, et al. Diabetes Care 2011
Genotyping

Nineteen type 2 diabetes-susceptibility SNPs (Taqman), 8 of them associated with insulin secretion

PPARG rs1801282, KCNJ11 rs5219, TCF7L2 rs7903146
SLC30A8 rs13266634, HHEX rs1111875, CDKN2B rs10811661
IGF2BP2 rs4402960, CDKAL1 rs7754840, FTO rs9939609
HNF1B rs757210, WFS1 rs10010131, JAZF1
rs864745, CDC123 rs12779790
TSPAN8 rs7961581, THADA rs7578597, ADAMTS9 rs4607103
NOTCH2 rs10923931, KCNQ1 rs2283228, MTNR1B rs10830963
Impact of FH and Genetic Risk Variants

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Family history of T2DM</td>
<td>0.78</td>
<td>(0.57; 1.06)</td>
<td>0.118</td>
</tr>
<tr>
<td>Genetic risk score (19 SNPs)</td>
<td>1.04</td>
<td>(0.90; 1.20)</td>
<td>0.617</td>
</tr>
<tr>
<td>Intervention vs. control group</td>
<td>0.55</td>
<td>(0.41; 0.75)</td>
<td>1.2E-04</td>
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<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Family history of T2DM</td>
<td>0.80</td>
<td>(0.57; 1.11)</td>
<td>0.180</td>
</tr>
<tr>
<td>Genetic risk score (19 SNPs)</td>
<td>1.02</td>
<td>(0.87; 1.18)</td>
<td>0.840</td>
</tr>
<tr>
<td>Intervention vs. control group</td>
<td>0.52</td>
<td>(0.38; 0.72)</td>
<td>5.9E-05</td>
</tr>
<tr>
<td>Fasting glucose (baseline)</td>
<td>1.69</td>
<td>(1.44; 1.99)</td>
<td>2.2E-10</td>
</tr>
<tr>
<td>2-h glucose (baseline)</td>
<td>1.35</td>
<td>(1.14; 1.60)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Fasting insulin (baseline)</td>
<td>1.25</td>
<td>(1.03; 1.53)</td>
<td>0.025</td>
</tr>
<tr>
<td>2-h insulin (baseline)</td>
<td>0.81</td>
<td>(0.63; 1.02)</td>
<td>0.076</td>
</tr>
<tr>
<td>BMI (baseline)</td>
<td>1.17</td>
<td>(0.98; 1.39)</td>
<td>0.077</td>
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</table>
## Progressors vs non-progressors to T2D

<table>
<thead>
<tr>
<th></th>
<th>Progressors (143)</th>
<th>Non-progressors (312)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>31.9 ± 5.1</td>
<td>29.4 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Δ BMI first year</strong></td>
<td>-0.87 (-1.16; -0.57)</td>
<td>-1.21 (-1.39; -1.02)</td>
<td>0.04</td>
</tr>
<tr>
<td>Matsuda ISI†</td>
<td>3.16 (2.88; 3.44)</td>
<td>4.40 (4.19; 4.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIGR&lt;sub&gt;0-30&lt;/sub&gt;</td>
<td>31.0 (28.1; 33.8)</td>
<td>31.9 (30.0; 33.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>ISI-adjusted AIGR&lt;sub&gt;0-30&lt;/sub&gt;†</td>
<td>22.0 (20.8; 23.2)</td>
<td>32.5 (31.4; 33.5)</td>
<td>&lt;0.001</td>
</tr>
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</table>

* For the effect of diabetes during the follow-up (progressor or non-progressor) after univariate ANOVA, GLM adjusted for age, sex and study group.

† Progressors, n=141 and non-progressors, n=310.

De Mello et al. Diabetes Care 2012
Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS)

J. Lindström · M. Peltonen · J. G. Eriksson · P. Ilanne-Parikka · S. Aunola · S. Keinänen-Kiukaanniemi · M. Uusitupa · J. Tuomilehto · for the Finnish Diabetes Prevention Study (DPS)

Received: 31 May 2012 / Accepted: 7 September 2012
© Springer-Verlag Berlin Heidelberg 2012
Incidence of Diabetes after 13 years of follow-up, Lindström J et al. Diabetologia 2013

Adjusted HR: Adjusted for sex, age, 2h glucose and BMI at baseline.
The DPS: The more goals achieved, the lower the risk!

- Weight reduction > 5%
- Moderate fat <30 E%
- Low saturated fat <10 E%
- High fibre >15g/1000kcal
- Physical activity >30 min /day

Goals at year 3; incidence during 13 years time-span
Adjusted for baseline age, bmi, 2h-glucose and sex

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

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

Lindström et al. Diabetologia. 2013
DEHKO 2000–2010

Primary Prevention of Type 2 Diabetes

- Programme for the Prevention of Type 2 Diabetes (2003–2010)
  - Population Strategy
  - High-Risk Strategy
  - Strategy of Early Diagnosis and Management
- Implementation of the Prevention Programme: FIN-D2D Project 2003–2007

Developing Diabetes Care and its Quality

- Care Organization
- Quality Criteria and Quality Monitoring Systems
- Basic Education and Further Training of Health Care Staff
- Modern Medication

Supporting Self-Care of Persons with Diabetes

- Education
- Rehabilitation
- Peer Support
- Cooperation with Finnish Diabetes Associations
- Local Branches

Influencing Municipal Decision-making
FIN-D2D: Positive experiences

• Models of lifestyle intervention were proven feasible in primary health care

• **Screening and risk assessment** became part of daily practice:
  – The FINDRISC; OGTT testing; waist circumference measurement

• **Treatment paths** were defined and health promotion units were established in all participating hospital districts

• **New ways of collaboration**
  – Multi-professional team work
  – Hospital districts, municipalities, health care centres, occupational health care, NGOs, pharmacies, research organizations

• **Nationwide recognition and increased awareness of obesity and diabetes problem**
Central idea of StopDia project:
Three levels of action to stop diabetes

1. **Individuals**: reach all and motivate in lifestyle changes
2. **Living environment**: modify to support healthy lifestyle
3. **Society**: Identify barriers and facilitators
Incidence of diagnosed diabetes


Finland, 1994-2014: https://www.julkari.fi/handle/10024/125827
Two-year physical activity and dietary intervention effect on worsening insulin sensitivity in prepubertal and mainly normal weight children

Insulin resistance (HOMA-IR)

Baseline 2-year follow-up

Children in the intervention group

0.99 (0.87, 1.11) + 34%

1.03 (0.88, 1.17)

Children in the control group

1.33 (1.17, 1.42) + 46%

1.50 (1.36, 1.64)

P=0.018 for group x time interaction

~ 30%

Lakka TA et al. unpublished 2018
## Practical implementations

<table>
<thead>
<tr>
<th>Individual</th>
<th>Primary Health Care/District</th>
<th>Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness of the risk, screening (risk questionnaire)</td>
<td>Active screening of high risk individuals, gestational diabetes</td>
<td>County or national programmes to increase the awareness of T2DM</td>
</tr>
<tr>
<td>Positive family history, gestational diabetes</td>
<td>Training of health care staff (dietitians, nurses and physicians), motivation</td>
<td>Learning good practices from other stakeholders, investing in prevention facilities (including physical activity, healthy diet)</td>
</tr>
<tr>
<td>Permanent lifestyle changes, motivation</td>
<td>Increasing awareness of T2DM Investing into facilities</td>
<td>Taxation, food labeling, promoting physical activity in everyday life, healthy school lunches!</td>
</tr>
</tbody>
</table>
Conclusions

1. * We have unequivocal evidence that T2D is preventable by changing lifestyles, i.e. weight reduction, changing diet according to the current recommendations in terms of quality of fat, fiber intake (whole grain) and increased use of fruit and vegetables
2. * Risk reduction of T2D is strongly related to the degree of long-term weight loss and adherence to lifestyle changes, and the preventive effect has been demonstrated to sustain for many years after the active intervention
3. *Successful lifestyle intervention seems to overcome the impact of family history and genetic risk of T2DM
4. *Regarding gene-lifestyle interactions, prospective intervention studies are needed to confirm the DPS/DPP results
Healthy dietary patterns work

Britain could lower its rates of cancer, diabetes and cardiovascular disease by embracing Mediterranean- or Nordic-style diets, a major study into the benefits of healthy eating suggests (Guardian 2018)
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Figure 1. Cumulative incidence of total CVD in the DPS and FINRISK studies
Uusitupa et al. PLOS One 2009
Fresh fruit consumption in relation to incident diabetes and diabetic vascular complications: A 7-y prospective study of 0.5 million Chinese Adults, Du H et al. PLoS Med 2017