2016

Online Companion Document

PREVENTION AND SCREENING FOR TYPE 2 DIABETES

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A. CHRSP Synthesis Methods

Research Design & Publication Dates

The CHRSP topic for this project originated from the Department of Health and Community Services Newfoundland and Labrador. The department expressed interest in evidence surrounding type 2 diabetes management and prevention. This topic relates to a report released by the department in 2011 entitled *Improving Health Together: A Policy Framework for Chronic Disease Prevention and Management in Newfoundland and Labrador*. The framework consists of six key policy statements with three main outcomes. ***Prevention and Awareness*** of chronic disease is encompassed under policy statement #2 through the promotion of health and prevention of disease. Earlier detection and reduced progression of chronic disease is also one of three outcomes covered in the framework. Through discussion with the CHRSP team the project decided on the following research question:

"*What interventions are likely to be effective in reducing the incidence of Type 2 Diabetes and its medical complications in the adult population of Newfoundland and Labrador?"*

Our synthesis includes two types of research articles:

1) Systematic reviews, meta-analyses or health technology assessments published between June 2009 and June 2014, inclusive. To be considered a "systematic" a given review had to provide three things:
    i. a documented search strategy for identifying relevant primary studies;
    ii. citation info for all included studies; and
    iii. an aggregate description of included study characteristics that included participants, setting, intervention, outcomes.
2) Randomized controlled trials (RCTs) or cohort studies published between November, 2014 and June 13, 2014.

Selection Criteria for Literature Synthesis

The following Inclusion/Exclusion criteria were outlined as parameters for study selection. These were determined in consultation with the project team.

Table 1: Inclusion/exclusion criteria for literature synthesis

Inclusion/Exclusion Criteria	Systematic Literature	Primary Literature
Research Design	Include 'systematic' literature (reviews, meta-analyses or health technology assessments) that provide: • a documented search strategy for identifying relevant primary studies; • citation info for all included studies; and • an aggregate description of included study characteristics that included participants, setting, intervention, outcomes.	Include Randomized Controlled Trials, Prospective Cohort Studies.

Publication Date	Include if published June 13, 2009 – June 13, 2014.	Include if published November, 2009 – June 13, 2014 and not captured in the systematic literature.
Language	Include if article is in English	
Population	Include Population for **Primary Prevention** Literature if: • Adults ≥ 18 years old at-risk for Type 2 Diabetes, • In the case of a multi-site study, interventions delivered exclusively to adults at-risk for T2D are analyzed and evaluated separately from alternative populations, such that the reviewer can discern a finding or findings specific to an intervention and population of interest or if less than 1/3 of the population of a systematic review has T2D. **OR** Include Population for **Secondary Prevention** Literature if: • Asymptomatic Adults ≥ 18 years old at-risk for T2D, or • Adults with T2D are diagnosed through screening, or • In the case of a multi-site study, interventions are delivered exclusively to asymptomatic adults at risk for T2D, or adults with T2D diagnosed through screening are analyzed and evaluated separately from the others, such that the reviewer can discern a finding or findings specific to intervention and population of interest. • Exclude Screening for pregnant women with Gestational Diabetes	
Intervention	• Include articles relating to the effects of classes/categories of medications on preventing diabetes will be included. • Exclude articles relating to the effects of specific medications on preventing diabetes will be excluded. • Exclude articles relating to screening or early detection of type 1 diabetes or gestational diabetes.	
Outcome	• Include studies that measure the effect of interventions on diabetes-related complications, diabetes management for those detected through screening, and measure the cost of interventions. • Exclude Studies/reviews that evaluate diabetes risk assessment instruments, *unless* they directly measure the effect of such instruments on diabetes-related complications and diabetes management (as opposed to measuring just the reliability/validity/feasibility of a given risk assessment tool). • Exclude studies/reviews that evaluate the accuracy specific screening tests, *unless* they directly measure the effect of such tests on diabetes- related complications and diabetes management (as opposed to measuring just the sensitivity/specificity/ of a given screening test).	
Setting	Primary Care Setting Public	

Search Strategy and Article Selection

Relevant articles in periodical indexes PubMed, CINAHL and EMBASE were identified using the Boolean operator "AND" to combine sets of search terms: (1) subject headings and keywords related to adults at risk for T2D or asymptomatic adults, (2) subject headings and keywords related to primary and

secondary prevention interventions, and (3) a validated search filter for retrieving either systematic reviews or primary studies. Our search was limited to articles published in English for a five year span between June 2009 and June 2014 for systematic Literature. A primary literature search spanned November 2013 to June 2014 to capture any articles not covered by the included systematic literature. Additional searches in the Cochrane Library, Econlit and grey literature websites were also conducted. The tables that follow illustrate how search strategy was constructed. In order to limit article retrieval to the desired types of research design, each search employs and evidence-based research-validated search filter designed by the Health Information Research Unit at McMaster University.

Pubmed Search Strategy

Table 2: Pubmed search strategy for systematic and primary literature

Pre-diabetic concept	("Hyperglycemia"[Majr] OR "hyperglycemia"[title]) OR ("Prediabetic State"[Majr]) OR ("Glucose Intolerance"[Majr] OR "glucose intolerance"[title]) OR ("Diabetes Mellitus, Type 2"[Majr] OR "diabete*"[Title] OR "type 2 diabetes"[Title])
Prevention concept	("Primary Prevention"[Majr] OR "Secondary Prevention"[Majr] OR "prevent*"[TIAB] OR "Preventive health services"[Majr] OR "Health promotion"[Majr]) OR "Risk Reduction Behavior"[Majr] OR ("Mass Screening"[Majr] OR "screening"[TIAB]) OR ("Life Style"[Majr] OR "Lifestyle"[TIAB]) OR ("Diet"[Majr] OR "diet"[Title]) OR ("Incidence"[Mesh] OR "incidence"[title]) OR "Diabetes Mellitus, Type 2/prevention and control"[Majr])
Economics concept	("economic analysis"[tiab] OR ("Quality-adjusted life years"[Mesh] OR "Quality-adjusted life years"[tiab] OR "QALY"[tiab]) OR "Markov Model"[tiab] OR "costs and cost analysis"[MeSH] OR "costs"[tiab] OR "cost effective*"[tiab] OR "cost-benefit analysis"[MeSH] OR "health care costs"[MeSH] OR "cost-utility analysis"[tiab])
Systematic Reviews Prevention	
Limits	Filters: Abstract; Publication date from 2009/06/13 to 2014/06/13; English
Search string	((((("Hyperglycemia"[Majr] OR "hyperglycemia"[title]) OR ("Prediabetic State"[Majr]) OR ("Glucose Intolerance"[Majr] OR "glucose intolerance"[title]) OR ("Diabetes Mellitus, Type 2"[Majr] OR "diabete*"[Title] OR "type 2 diabetes"[Title]))) AND (("Primary Prevention"[Majr] OR "Secondary Prevention"[Majr] OR "prevent*"[TIAB] OR "Preventive health services"[Majr] OR "Health promotion"[Majr]) OR "Risk Reduction Behavior"[Majr] OR ("Mass Screening"[Majr] OR "screening"[TIAB]) OR ("Life Style"[Majr] OR "Lifestyle"[TIAB]) OR ("Diet"[Majr] OR "diet"[Title]) OR ("Incidence"[Mesh] OR "incidence"[title]) OR "Diabetes Mellitus, Type 2/prevention and control"[Majr])) AND (("meta-analysis"[Publication Type] OR "meta-analysis"[tiab] OR "review"[Publication Type] OR "search*"[tiab] OR "systematic review"[tiab] OR systematic[sb]))
Results	1013
Primary Literature Prevention	
Limits	Abstract; Publication date from 2013/09/01 to 2014/06/13; English
Search String	((((("Hyperglycemia"[Majr] OR "hyperglycemia"[title]) OR ("Prediabetic State"[Majr]) OR ("Glucose Intolerance"[Majr] OR "glucose intolerance"[title]) OR ("Diabetes Mellitus, Type 2"[Majr] OR "diabete*"[Title] OR "type 2 diabetes"[Title]))) AND (("Primary Prevention"[Majr] OR "Secondary Prevention"[Majr] OR "prevent*"[TIAB] OR "Preventive health services"[Majr] OR "Health promotion"[Majr]) OR "Risk Reduction Behavior"[Majr] OR ("Mass Screening"[Majr] OR "screening"[TIAB]) OR ("Life Style"[Majr] OR "Lifestyle"[TIAB]) OR ("Diet"[Majr] OR "diet"[Title]) OR ("Incidence"[Mesh] OR "incidence"[title]) OR "Diabetes Mellitus, Type 2/prevention and control"[Majr])) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR

	clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
Results	412 (Retrieved September 23, 2014)
Systematic Reviews Economic	
Limits	Filters: Abstract; Publication date from 2009/06/13 to 2014/06/13; English
Search string	(((((("Hyperglycemia"[Majr] OR "hyperglycemia"[title]) OR ("Prediabetic State"[Majr]) OR ("Glucose Intolerance"[Majr] OR "glucose intolerance"[title]) OR ("Diabetes Mellitus, Type 2"[Majr] OR "diabete*"[Title] OR "type 2 diabetes"[Title]))) AND (("Primary Prevention"[Majr] OR "Secondary Prevention"[Majr] OR "prevent*"[TIAB] OR "Preventive health services"[Majr] OR "Health promotion"[Majr]) OR "Risk Reduction Behavior"[Majr] OR ("Mass Screening"[Majr] OR "screening"[TIAB]) OR ("Life Style"[Majr] OR "Lifestyle"[TIAB]) OR ("Diet"[Majr] OR "diet"[Title]) OR ("Incidence"[Mesh] OR "incidence"[title]) OR "Diabetes Mellitus, Type 2/prevention and control"[Majr])) AND (("economic analysis"[tiab] OR ("Quality-adjusted life years"[Mesh] OR "Quality-adjusted life years"[tiab] OR "QALY"[tiab]) OR "Markov Model"[tiab] OR "costs and cost analysis"[MeSH] OR "costs"[tiab] OR "cost effective*"[tiab] OR "cost-benefit analysis"[MeSH] OR "health care costs"[MeSH] OR "cost-utility analysis"[tiab]))) AND ((("meta-analysis"[Publication Type] OR "meta-analysis"[tiab] OR "review"[Publication Type] OR "search*"[tiab] OR "systematic review"[tiab] OR systematic[sb])))
Results	79
RCTs Economic	
Limits	Filters: Abstract; Publication date from 2009/06/13 to 2014/06/13; English
Search string	(((((("Hyperglycemia"[Majr] OR "hyperglycemia"[title]) OR ("Prediabetic State"[Majr]) OR ("Glucose Intolerance"[Majr] OR "glucose intolerance"[title]) OR ("Diabetes Mellitus, Type 2"[Majr] OR "diabete*"[Title] OR "type 2 diabetes"[Title]))) AND (("Primary Prevention"[Majr] OR "Secondary Prevention"[Majr] OR "prevent*"[TIAB] OR "Preventive health services"[Majr] OR "Health promotion"[Majr]) OR "Risk Reduction Behavior"[Majr] OR ("Mass Screening"[Majr] OR "screening"[TIAB]) OR ("Life Style"[Majr] OR "Lifestyle"[TIAB]) OR ("Diet"[Majr] OR "diet"[Title]) OR ("Incidence"[Mesh] OR "incidence"[title]) OR "Diabetes Mellitus, Type 2/prevention and control"[Majr])) AND (("economic analysis"[tiab] OR ("Quality-adjusted life years"[Mesh] OR "Quality-adjusted life years"[tiab] OR "QALY"[tiab]) OR "Markov Model"[tiab] OR "costs and cost analysis"[MeSH] OR "costs"[tiab] OR "cost effective*"[tiab] OR "cost-benefit analysis"[MeSH] OR "health care costs"[MeSH] OR "cost-utility analysis"[tiab]))) AND (((randomized controlled trial[Publication Type] OR randomized [Title/Abstract] OR placebo[Title/Abstract])))
Results	51

CIHNAL Search Strategy

Table 3: CIHNAL search strategy

Pre-diabetic concept	(MM "Hyperglycemia") OR "hyperglycemia" OR (MM "Prediabetic State)" OR "prediabetic state" OR (MM "Glucose Intolerance") OR "glucose intolerance" OR (MM "Diabetes Mellitus, Type 2") OR "type 2 diabetes" OR TI diabete*
Prevention concept	(MM "Health Screening" OR TI screening) OR (MM "Preventive Health Care" OR TI prevent* OR MM "Health Promotion") OR (MM "Life Style Changes" OR TI Lifestyle) OR (MM "Diet Therapy") OR "diet") OR (MM "Incidence" OR "incidence")
Economics concept	(MM "Cost Savings") OR (MM "Cost Benefit Analysis") OR "cost" OR (MM "Costs and Cost Analysis")

Systematic Reviews Prevention	
Limits	**Limiters** - Abstract Available; Published Date: 20090601-20140631; Exclude MEDLINE records; Clinical Queries: Review - High Sensitivity
Search string	(MM "Hyperglycemia") OR "hyperglycemia" OR (MM "Prediabetic State") OR "prediabetic state" OR (MM "Glucose Intolerance") OR "glucose intolerance" OR(MM "Diabetes Mellitus, Type 2") OR "type 2 diabetes" OR TI diabete* AND TI screening OR (MM "Preventive Health Care" OR TI prevent* OR MM "Health Promotion") OR (MM "Life Style Changes" OR TI: Lifestyle) OR (MM "Diet Therapy") OR "diet") OR (MM "Incidence" OR "incidence") AND Abstract Available; Published Date: 20090601-20140631; Exclude MEDLINE records; Clinical Queries: Review - High Sensitivity
Results	68
Primary Literature Prevention	
Limits	**Limiters** - Published Date: 20131101-20140631; English Language; Exclude MEDLINE records; Clinical Queries: Prognosis - High Sensitivity OR **Limiters** - Abstract Available; Published Date: 20131101-20140631; English Language; Exclude MEDLINE records; Clinical Queries: Therapy - High Sensitivity
Search String	(MM "Hyperglycemia") OR "hyperglycemia" OR (MM "Prediabetic State") OR "prediabetic state" OR (MM "Glucose Intolerance") OR "glucose intolerance" OR(MM "Diabetes Mellitus, Type 2") OR "type 2 diabetes" OR TI diabete* AND TI screening OR (MM "Preventive Health Care" OR TI prevent* OR MM "Health Promotion") OR (MM "Life Style Changes" OR TI: Lifestyle) OR (MM "Diet Therapy") OR "diet") OR (MM "Incidence" OR "incidence") AND Abstract Available; Published Date: 20131101-20140631; English Language; Exclude MEDLINE records; Clinical Queries: Prognosis - High Sensitivity OR Abstract Available; Published Date: 20131101-20140631; English Language; Exclude MEDLINE records; Clinical Queries: Therapy - High Sensitivity
Results	(Retrieved September 29, 2014)60 total 27 overlap = 33 independent results
Economic	
Limits	Abstract Available; Published Date: 20090601-20140631; English Language; Exclude MEDLINE records; Language: English
Search string	(MM "Hyperglycemia") OR "hyperglycemia" OR (MM "Prediabetic State") OR "prediabetic state" OR (MM "Glucose Intolerance") OR "glucose intolerance" OR(MM "Diabetes Mellitus, Type 2") OR "type 2 diabetes" OR TI diabete* AND TI screening OR (MM "Preventive Health Care" OR TI prevent* OR MM "Health Promotion") OR (MM "Life Style Changes" OR TI: Lifestyle) OR (MM "Diet Therapy") OR "diet") OR (MM "Incidence" OR "incidence") AND Abstract Available; Published Date: 20090601-20140631; English Language; Exclude MEDLINE records; Language: English
Results	37

Embase Search Strategy

Table 4: Embase search strategy

Pre-diabetic concept	('hyperglycemia'/mj OR 'hyperglycemia':ti OR 'hyperglycemia':ab) OR ('impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti OR 'impaired glucose tolerance':ab) OR ('prediabetes':ti OR 'prediabetes':ab) OR ('non insulin dependent diabetes mellitus'/mj OR 'type 2 diabetes':ti)
Prevention concept	('mass screening'/mj OR 'screening'/mj OR 'screening':ti OR 'screening':ab) OR ('prevention'/mj OR 'prevention':ti OR 'prevention':ab OR 'primary prevention'/mj OR 'secondary prevention'/mj) OR ('lifestyle modification'/mj OR 'lifestyle':ti) OR ('diet'/mj OR 'diet':ti OR 'diet':ab) OR ('incidence'/mj OR 'incidence':ti) OR ('prevention and control'/mj) OR ('risk reduction'/mj)
Economics concept	(economic:ti OR economic:ab OR cost*ti OR cost:ab)
Systematic Reviews Prevention	
Limits	([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([article]/lim OR [review]/lim) AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [6-6-2009]/sd NOT [6-6-2014]/sd AND [2009-2014]/py
Search string	('hyperglycemia'/mj OR 'hyperglycemia':ti OR 'hyperglycemia':ab) OR ('impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti OR 'impaired glucose tolerance':ab) OR ('prediabetes':ti OR 'prediabetes':ab)OR ('non insulin dependent diabetes mellitus'/mj OR 'type 2 diabetes':ti) AND ('mass screening'/mj OR 'screening'/mj OR 'screening':ti OR 'screening':ab) OR ('prevention'/mj OR 'prevention':ti OR 'prevention':ab OR 'primary prevention'/mj OR 'secondary prevention'/mj) OR ('lifestyle modification'/mj OR 'lifestyle':ti) OR ('diet'/mj OR 'diet':ti OR 'diet':ab) OR ('incidence'/mj OR 'incidence':ti) OR ('prevention and control'/mj) OR ('risk reduction'/mj)
Results	155
Primary Search	
Limits	'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled study'/de OR 'intervention study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de AND [english]/lim AND [abstracts]/lim AND [1-11-2013]/sd NOT [13-6-2014]/sd AND **'human'**/de
Search String	('hyperglycemia'/mj OR 'hyperglycemia':ti OR 'hyperglycemia':ab) OR ('impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti OR 'impaired glucose tolerance':ab) OR ('prediabetes':ti OR 'prediabetes':ab)OR ('non insulin dependent diabetes mellitus'/mj OR 'type 2 diabetes':ti) AND ('mass screening'/mj OR 'screening'/mj OR 'screening':ti OR 'screening':ab) OR ('prevention'/mj OR 'prevention':ti OR 'prevention':ab OR 'primary prevention'/mj OR 'secondary prevention'/mj) OR ('lifestyle modification'/mj OR 'lifestyle':ti) OR ('diet'/mj OR 'diet':ti OR 'diet':ab) OR ('incidence'/mj OR 'incidence':ti) OR ('prevention and control'/mj) OR ('risk reduction'/mj) AND ('clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled study'/de OR 'intervention study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de AND [english]/lim AND [abstracts]/lim AND [1-11-2013]/sd NOT [13-6-2014]/sd)

	AND **'human'**/de
Results	431
Economic	
Limits	[abstracts]/lim AND [embase]/lim AND [2009-2014]/py
Search string	('hyperglycemia'/mj OR 'hyperglycemia':ti OR 'hyperglycemia':ab) OR ('impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti OR 'impaired glucose tolerance':ab) OR ('prediabetes':ti OR 'prediabetes':ab)OR ('non insulin dependent diabetes mellitus'/mj OR 'type 2 diabetes':ti) AND ('mass screening'/mj OR 'screening'/mj OR 'screening':ti OR 'screening':ab) OR ('prevention'/mj OR 'prevention':ti OR 'prevention':ab OR 'primary prevention'/mj OR 'secondary prevention'/mj) OR ('lifestyle modification'/mj OR 'lifestyle':ti) OR ('diet'/mj OR 'diet':ti OR 'diet':ab) OR ('incidence'/mj OR 'incidence':ti) OR ('prevention and control'/mj) OR ('risk reduction'/mj) AND (economic:ti OR economic:ab OR cost*ti OR cost:ab)
Results	466

ECONLIT Search Strategy

Table 5: ECONLIT search strategy

Economic	
Prevention Concept	diabetes prevention diabetes screening
Economic String	((SU.exact("BENEFIT COST ANALYSIS") OR SU.exact("COST BENEFIT ANALYSIS") OR SU.exact("COST BENEFIT ANALYSIS") OR SU.exact("COST BENEFIT ANALYSES") OR SU.exact("COST BENEFIT ANALYSIS 03601") OR SU.exact("COST BENEFIT ANALYSES") OR SU.exact("COST BENEFIT ANALYSIS")) AND SU.exact("DIABETES MELLITUS TYPE 2"))
	diabetes AND prevention diabetes AND screening
Limits	(Limiters: Published Date: 20090601-20140631 Publication Type: Journal Article)
Results	Searched diabetes prevention = 3/4 results for FTR Searched diabetes screening = 7 results, 1 relevant found above Searched diabetes AND prevention = 1/ 8 results for FTR, 3 other results duplicated Searched diabetes AND screening = 8, 1 duplicate result

Cochrane Search Strategy

Table 6: Cochrane search strategy

Cochrane Library Search	
Prevention Concept	Diabetes Mellitus, Type 2 Prevention
String	diabetes AND prevention diabetes AND screening
Limits	(Limiters: Published Date: 2009-2014)
Results	9 for Full Text Review

Grey lit search

Note: If the grey lit search turned up an article we'd already identified, we did not list it here

I. CANADA

- CADTH (http://www.cadth.ca/en/products) – Date Searched - July 3rd 2014
  Search for "diabetes prevention" and "diabetes screening" in "All Products"
  Results: 160 Selected: 1
  - CADTH, 2013: Diabetes Screening for Asymptomatic Adults: A Review of the Diagnostic Accuracy, Cost Effectiveness, and Guidelines (downloaded)
- Evidence-Informed Healthcare Renewal Portal (www.eihrportal.org) – Date Searched - July 3rd 2014
  Search for "diabetes prevention or diabetes screening "in title, abstract, and synonym fields – limited to 2009-2014, systematic reviews.
  Results: 21, 19 Selected: 3 (2 for FTR, 1 for Primary)
  - Dalsgaard EM, Christensen JO, Skriver MV, Borch JK, Lauritzen T, Sandbaek A. Comparison of different stepwise screening strategies for type 2 diabetes: Finding from Danish general practice, Addition-DK. Primary Care Diabetes. 2010;4(4):223-229.
  - Glechner A, Harreiter J, Rohleder S, Kautzky A, Van Noord MG, Kaminski-Hartenthaler A, et al. Gender-related differences in diabetes prevention. PROSPERO. 2012. (http://www.crd.york.ac.uk/NIHR_PROSPERO/display_record.asp?ID=CRD42012003102#.U7WGpfldXHV)
    - Completed but not published
  - Herman WH, Edelstein SL, Ratner RE, Montez MG, Ackermann RT, Orchard TJ, et al. Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. American Journal of Managed Care. 2013;19(3):194-202. ECONOMIC
    - (http://www.ncbi.nlm.nih.gov/pubmed/23544761)
  - Khunti K, Gillies CL, Taub NA, Mostafa SA, Hiles SL, Abrams KR, et al. A comparison of cost per case detected of screening strategies for Type 2 diabetes and impaired glucose regulation: Modelling study. Diabetes Research and Clinical Practice. 2012;97(3):505-513. ECONOMIC
    - (http://www.ncbi.nlm.nih.gov/pubmed/22554999)
- healthevidence.org (http://www.healthevidence.org/search.aspx) – Date Searched - July 3rd 2014
  Search for "diabetes prevention or diabetes screening " – limited to 2009-2014.
  Results: 57, 26 **Selected:** 2
  - Greaves CJ, Sheppard KE, Abraham C, Hardeman W, Roden M, Evans PH, & Schwarz P. (2011). Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health*, *11*, 119-131. PREVENTION (http://www.ncbi.nlm.nih.gov/pubmed/21333011?dopt=Abstract)
  - Malkawi AM. (2012). The effectiveness of physical activity in preventive type 2 diabetes in high risk individuals using well- structures interventions: A systematic review.*Journal of Diabetology*, *2*, 1-18. (http://www.journalofdiabetology.org/Pages/Releases/PDFFiles/EIGHTISSUE/RA-1-JOD-12-002.pdf)
    - Exclude – population not well defined (doesn't discuss age of participants). Also it is really a lit review not a systematic review

- Jackson L. (2009). Translating the diabetes prevention program into practice: A review of community interventions. *The Diabetes Educator*, *35*(2), 309-320. (http://www.ncbi.nlm.nih.gov/pubmed/19321809?dopt=Abstract)

- PATH (http://www.path-hta.ca/Publications-Presentations/Publications/Al.aspx) – Date Searched - July 3rd 2014
  Searched Report section manually 2009-2014
  Results: 26 **Selected:** 0
- CHEPA (http://www.chepa.org/research-products/search-for-documents) – Date Searched - July 3rd 2014
  Search for "diabetes" in publications database
  Results: 0 **Selected:** 0
- AETMIS (http://www.inesss.qc.ca/index.php?id=49) – Date Searched - July 4, 2014
  Publication search 2009-2014
  Searched for "diabetes screening"
  Results: 1 Selected: 0
  Searched for "type 2 diabetes"
  Results: 5 Selected: 0
- TAU of the MUHC (http://www.mcgill.ca/tau/publications) – Date Searched - July 4, 2014
  Search all products
  Results: 2 pages of results Selected: 0 – None relevant to screening
- MCHP (http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html) – Date Searched - July 4, 2014
  Manual search
  Results: 21 Selected: 0 – None relevant
- IHE (http://www.ihe.ca/publications/library/) – Date Searched - July 4, 2014
  Publication search by description 2009-2014
  Searched Publication by year **Selected:** 0
- ARCHE (http://www.ualberta.ca/ARCHE/publications.htm) – Date Searched - July 4, 2014
  Manual search by Publication title
  Results: 7 (Mainly Gestational Diabetes) **Selected:** 0
- CHSPR (http://chspr.ubc.ca/pubs/pub-search) – Date Searched - July 4, 2014
  Manual search
  Results: 3 **Selected:** 0
- Public Health Agency of Canada (http://www.phac-aspc.gc.ca/index-eng.php) – Date Searched - July 4, 2014
  Searched publications and reports by Major topic area 2009-2014: Diabetes
  Results: 4 **Selected: 3 (Background)**
  - PHAC, 2011. Diabetes in Canada: Facts and figures from a public health perspective. http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/index-eng.php
  - Diabetes Care Program of Nova Scotia (on behalf of the NS Prediabetes Project Team) Canadian Diabetes Association. 2009. Upstream screening and community intervention for prediabtes and undiagnosed type 2 diabetes. Final Report, Diabetes Care Program of Nova Scotia.
  - Canadian Task Force on Preventive Health. 2012. Recommendations on screening for type 2 diabetes in adults. Canadian Medical Association Journal, 184(15), p1687-1696. http://canadiantaskforce.ca/ctfphc-guidelines/2012-type-2-diabetes/
- http://www.diabetes.ca/ - Date Searched - July 4, 2014
  Searched website for publications
  Selected: 7 (Background/Contexualization)
  - CDA - 2011 - NL Provinical Coverage Provisions
  - CDA - At the tipping point Diabetes in NL

- The Cost of Diabetes in NL
- CDA- 2014- Diabetes in NL
- CDA- The Burden of Out-of-pocket Costs for Canadians with Diabetes
- CDA-2009- An economic tsunami the cost of diabetes in Canada
- CDA-2011- Diabetes, Canada at the Tipping Point

II. U.K.

- National Health Service Evidence (http://www.evidence.nhs.uk/) – Date Searched - July 7, 2014
  Search for "diabetes screening" and "diabetes prevention" limited to last 5 years
  Results: Many **Selected:** 4 (Economic)
  - Chen L, Magliano DJ, Balkau B, Wolfe R, Brown L, Tonkin AM, Zimmet PZ, Shaw JE. Maximizing efficiency and cost-effectiveness of type 2 diabetes screening: the AusDiab study. Diabetic Medicine 2011; 28(4): 414-423
  - Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, Gregg E, Holman RR, Kirkman MS, Stern M, Tuomilehto J, Wareham NJ. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010; 375(9723): 1365-1374
  - Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabetologia 2010; 53(5): 875-881
- Healthcare Improvement Scotland (http://www.healthcareimprovementscotland.org/welcome_to_healthcare_improvem.aspx) – Date Searched - July 7, 2014
  Search for: "diabetes screening " in HTA reports and "diabetes prevention" in HTA reports
  Results: 2, 0 Selected: 0,0
- NIHR HTA Programme (http://www.hta.ac.uk/project/htapubs.asp) – Date Searched - July 7, 2014
  Manual search: HTA, SR, "diabetes screening" and "diabetes prevention
  Results: 0 **Selected:** 0
- University of Birmingham Health Services Management Centre (http://www.birmingham.ac.uk/schools/social-policy/departments/health-services-management-centre/publications/index.aspx) – Date searched Date Searched – July 7,2014

III. U.S.

- CTAF (http://www.ctaf.org/assessments) – Date Searched - July 7, 2014
  Manual search **Selected:** 0
- AHRQ (http://www.ahrq.gov/research/findings/index.html) – Date Searched - July 7, 2014
  Manual search of Evidence-based Practice Center Reports by Year
  Selected: 1
  - Sumamo E, Ha C, Korownyk C, Vandermeer B, Dryden DM. Lifestyle interventions for four conditions: type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. Rockville, MD, USA: Agency for Healthcare Research and Quality. AHRQ Technology Assessment Program. 2011

  Manual search of Full Research Reports
  Selected: 0
- NY Academy of Medicine Library Catalog (http://nyam.waldo.kohalibrary.com/cgi-bin/koha/opac-search.pl) – Date Searched - July 7, 2014
  Search for "diabetes prevention" in title keywords and "diabetes screening", English, 2009-2014
  Selected: 0

- CMS (http://www.cms.gov/medicare-coverage-database/indexes/technology-assessments-index.aspx?bc=BAAAAAAAAAAA&) – Date searched – July 7, 2014
  Manual search
  Selected: 0
- United States Centers for Disease Control and Prevention http://www.cdc.gov/ - Date searched – July 7, 2014
  Results: **Selected: 3 for background**
  - CDC - 2011 - National Diabetes Fact Sheet
  - CDC- Diabetes Report Card 2012
  - CDC-2013- Effective Public Health Strategies to Prevent and Control Diabetes
- Institute of Medicine http://www.iom.edu/ - Date Searched - July 7, 2014
  Searched "diabetes"
  Results: 14 **Selected: 0**
- American Diabetes Association http://www.diabetes.org/ - Date searched - July 7, 2014
  Results: 0 **Selected: 0**
  Online descriptions but no reports

IV. Australia/New Zealand

- Australia and New Zealand Horizon Scanning Network (http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/technologies-assessed-lp-2) – July 7, 2014
  Manual search of Technologies Assessed:102
  Selected: 0
- Medical Services Advisory Committee (Gov of Australia) (http://www.msac.gov.au/internet/msac/publishing.nsf/Content/completed-assessments) – Date Searched - July 8, 2014
  Manual search of website searching for "diabetes prevention" or "diabetes screening" **Selected: 1 (Background)**
  - Australian Government, Department of Health. 2013. 1267 Final Decision Analytic Protocol (DAP) to guide the assessment of HbA1c testing for the diagnosis of diabetes mellitus.
- National Health and Medical Research Council (http://www.nhmrc.gov.au/guidelines-publications) – Date Searched - July 8, 2014
  Manual search for Diabetes category publications
  Results: 14 **Selected:** 1 (Background)
  - Colagiuri R, Girgis S, Gomez M, Walker K, Colagiuri S, O'Dea K. National Evidence Based Guideline for the Primary Prevention of Type 2 Diabetes. Diabetes Australia and the NHMRC, Canberra 2009.

V. International

- World Health Organization - Date Searched - July 8, 2014 http://www.who.int/en/
  Searched Diabetes section of website
  Selected: 3 (Background)
  - WHO. 2003. Screening for Type 2 Diabetes Report of a World Health Organization and International Diabetes Federation meeting. WHO/NMH/MNC/03.1.
  - WHO. 2011. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. WHO/NMH/CHP/CPM/11.1

Summary of Search Results and Included Articles:

Article Selection

Search: Our search for systematic reviews retrieved 1237 possible results from PubMed, CINAHL, and EMBASE. Our search for randomized controlled trials (RCTs) of the same databases retrieved possible 1675 citations.

Filtering by title/abstract: The title and abstracts of the retrieved systematic review citations were screened by one reviewer (SM) and checked by a second reviewer (AS). The title and abstracts of the retrieved RCT citations were screened by the SM. On this basis, 29 systematic reviews and 6 primary RCTs and 10 from grey literature were selected for full-text review.

Full Text Review: Using the selection criteria outlined above in Section B of this appendix, we selected 22 systematic reviews and 5 primary studies for inclusion in the synthesis.

Table 7: Summary of search results by database

Database Queried	Search Type	# Returned Articles	Full Text Review	Included Articles
Pubmed	Systematic	1013	54	17
	Primary	940	33	3
	Economic	79	26	4
CINAHL	Systematic	69	8	0
	Primary	51	3	0
	Economic	37	2	0
Embase	Systematic	155(duplicates included	17	3
	Primary	684	29	2
	Economic	466	12	5
Econlit	Economic	N/A	4	1
Higher School of Economics	Economic	N/A	2	1
Cochrane	All	N/A	35, 17 (with duplicates removed)	5 (Economic)
Grey Lit	All	N/A	10	2
			Total	43

Included Article Base: When we totaled up all the studies included in our selected reviews and eliminated duplicates, we determined that the primary research base covered by our synthesis encompasses 327 different studies. A certain number of these studies appeared in more than one review (see table below).

Table 8: Systematic review literature, primary overlap

	Primary Study Distribution Amongst Included Systematic Literature:						
	7 reviews	6 reviews	5 reviews	4 reviews	3 reviews	2 reviews	1 reviews
Number of Primary Studies	1: Ramachandran (2006)	3: Mensink (2003)a, Pan (1997), Tuomilehto (2001)	3: Chiasson (2002), Diabetes Prevention Program (2002)a, Knowler (2002)	1: Kawamori (2009)	15: Absetz (2007), Bo (2007), Brunner (2008), DREAM Trial (2006)b, Eriksson (1999), Fang (2004), Kosaka (2005), Laaksonen (2005), Laatikainen (2007), Lindstrom (2003)a, Lindstrom (2006), Martinez-Gonzalez (2008), Mozaffarian (2007), Oldroyd (2006), Roumen (2008)	51	253

Citations for Excluded Reviews

Table 9: Excluded reviews and reasons for their exclusion

Did not meet criteria for population	***Did not adhere to topic***	***Did not meet criteria for setting***	***Did not evaluate intervention outcomes or used risk measures for outcomes***	***Did not provide a search strategy or aggregate descriptions of studies***	***Did not separate primary and secondary prevention***	***Did not meet our criteria for systematic reviews***
Johnson (2011) Thompson (2009) Sumamo (2011) Korkiakangas (2009) Han (2012)	Herman (2011) Hollander (2012) Naci (2013) Esposito (2013) Rajpathak (2009) Bennett (2009) Li (2010)	Rawal (2012)	Carter (2010) Esposito (2010) Esposito (2014) Kolvoerou (2014) Pan (2011) Paulweber (2010) Ricci-Cabello (2010)	Southwood (2010) Walker (2010) Motamedi (2012)	Angermayr (2010)	Athyros (2010) Backholer (2012) Bergman (2013) Blonde (2011) Echouffo-Tcheugui (2011) Karam (2011) McEvoy (2012) Moutzouri (2011) Psaltopoulou (2010) Ambady (2013) Salas-Salvado (2011)

						Sanz (2010) Schwarz (2011) Schwarz (2010) Thomas (2010) Tuomilehto (2009) Verier-Mine (2010) Yacoub (2014) Bronas (2009) Lau (2013) Lamb (2013) Sievepiper (2013) Sharma (2011) Bhake (2010) Franz (2014) Ambady (2013) Maghsoudi (2012) Hershon (2011) Lee (2011) Schwarz (2011) Kastorini (2009) Steyn (2009) Jackson (2009) Gillett (2010) Nyenwe (2011) Taylor (2013)

Critical Appraisal

AMSTAR

As stated in the main report, our critical appraisal methodology for systematic reviews employs AMSTAR1, a validated measurement tool for evaluating the methodological quality of systematic reviews. Articles are scored on 11 items. Scores are expressed as a percentage out of 100%. Higher scores can be taken as an indicator that the various stages of the review – e.g., literature searching, pooling of data, critical appraisal, etc. – were conducted appropriately. Each included systematic review was scored independently by both Sarah Mackey (SM) and Adam Stacey (AS) using the AMSTAR tool. SM and AS then met and compared their appraisals, review by review, and resolved any discrepancies in score via a consensus procedure. Scores ranged from 27% to 100% on 11 items. SM extracted characteristics and findings from each review into a table with help from AS.

Below we provide a blank version of the AMSTAR scoring sheet, a table that illustrates how each review was scored, and the data extraction tables.

Table 10: AMSTAR scoring sheet

REFERENCE:

AMSTAR Item	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Table 11: Included systematic reviews, highest to lowest AMSTAR score

Review	AMSTAR Item											Total
	1	2	3	4	5	6	7	8	9	10	11	
Grant, 2009	1	1	1	1	1	1	1	1	1	1	1	11/11 (100%)
Schellenberg, 2013	1	1	1	1	0	1	1	1	1	1	1	10/11 (91%)
Gillett, 2012	1	1	1	0	1	1	1	1	1	1	0	9/11 (82%)
Sherifali, 2013	1	1	1	0	0	1	1	1	1	1	0	8/11 (73%)
Dunkley, 2014	0	1	1	0	0	1	1	1	1	1	0	7/11 (64%)
Dunkley, 2012	0	1	1	0	0	1	1	1	1	1	0	7/11 (64%)
Merlotti, 2014	0	1	1	0	0	1	1	1	1	1	0	7/11 (64%)
Phung, 2012	0	1	1	0	0	1	1	1	1	1	1	7/11 (64%)
Phung, 2011	0	1	1	0	0	1	1	1	1	1	0	7/11 (64%)
Yoon, 2013	0	1	1	0	0	1	1	1	1	1	0	7/11 (64%)
Aguiar, 2014	0	0	1	0	0	1	1	1	1	1	0	6/11 (55%)
Greaves, 2011	0	1	1	0	1	1	1	1	0	0	0	6/11 (55%)
Johnson, 2012	1	1	1	0	0	1	1	1	0	0	0	6/11 (55%)
Waugh, 2013	1	0	1	0	0	1	1	0	1	1	0	6/11 (55%)
Yuen, 2010	0	1	0	0	0	1	1	1	1	1	0	6/11 (55%)
Everson-Hock, 2013	0	0	1	0	0	1	1	1	1	0	0	5/11 (45%)
Geng, 2013	0	0	0	0	0	1	1	1	1	1	0	5/11 (45%)
Hopper, 2011	0	1	1	0	0	1	0	0	1	1	0	5/11 (45%)
Geng, 2012	0	0	0	0	0	1	1	1	1	0	0	4/11 (36%)
Shirani, 2013	0	0	1	0	0	1	0	0	1	1	0	4/11 (36%)
Song, 2012	0	1	0	0	0	1	0	0	1	1	0	4/11 (36%)
Malkawi, 2012	0	0	1	0	0	1	0	0	1	0	0	3/11 (27%)

Table 12: Overlap in the systematic review literature

Review/Amstar score	Total	Unique	Overlap	Percentage
Aguiar (2014) 55%	22	10	12	54.55
Dunkley (2014) 64%	25	13	12	48.00
Dunkley (2012) 64%	16	14	2	12.50
Everson (2013) 45%	34	34	0	0.00
Geng (2013) 45%	9	9	0	0.00
Geng (2012) 36%	11	4	7	63.64
Gillett (2012) 82%	14	6	8	57.14
Grant (2009) 100%	15	15	0	0.00
Greaves (2011) 55%	30	29	1	3.33
Hopper (2011) 45%	15	5	10	66.67
Johnson (2013) 55%	22	8	14	63.64
Malkawi (2012) 27%	17	6	11	64.71
Merlotti (2014) 64%	71	46	25	35.21
Phung (2012) 64%	13	6	7	53.85
Phung (2011) 64%	22	14	8	36.36
Schellenberg (2013) 91%	11	4	7	63.64
Sherifali (2013) 73%	5	5	0	0.00
Shirani (2013) 36%	7	7	0	0.00
Song (2012) 36%	11	5	6	54.55
Waugh (2013) 55%	4	4	0	0.00
Yoon (2013) 64%	23	11	12	52.17
Yuen (2010) 55%	4	0	4	100.00
Total	**401**	**255**	**146**	**36.41**

Downs and Black Checklist

As a second component in the critical appraisal the Downs and Black Checklist was used to evaluate included primary articles. Checklist components are included in the table below.

Table 13: Downs and Black Checklist

REPORTING	Yes/No/Partially	Score
1. Is the objective of the study clear?	Yes = 1, No = 0	
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes = 1, No = 0	
3. Are characteristics of the patients included in the study clearly described?	Yes = 1, No = 0	
4. Are the interventions clearly described?	Yes = 1, No = 0	
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes = 2 Partially = 1 No = 0	
6. Are the main findings of the study clearly described?	Yes = 1, No = 0	
7. Does the study estimate random variability in data for main outcomes?	Yes = 1, No = 0	
8. Have all the important adverse events consequential to the intervention been reported?	Yes = 1, No = 0	
9. Have characteristics of patients lost to follow-up been	Yes = 1, No = 0	
10. Have actual probability values been reported for the main outcomes except probability < 0.001?	Yes = 1, No = 0	
11. Is the source of funding clearly stated?*	Yes = 1, No = 0	
EXTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
12. Were subjects asked to participate in the study representative of the entire population recruited?	Yes = 1, No = 0, Unclear = 0	
13. Were those subjects who were prepared to participate representative of recruited	Yes = 1, No = 0, Unclear = 0	
14. Were staff, places, and facilities where patients were treated representative of treatment most received?	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
15. Was an attempt made to blind study subjects to the intervention?	Yes = 1, No = 0, Unclear = 0	
16. Was an attempt made to blind those measuring the main outcomes?	Yes = 1, No = 0, Unclear = 0	
17. If any of the results of the study were based on data dredging was this made clear?	Yes = 1, No = 0, Unclear = 0	
18. Was time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes = 1, No = 0, Unclear=0	

19. Were statistical tests used to assess main outcomes appropriate?	Yes = 1, No = 0, Unclear = 0	
20. Was compliance with the interventions reliable?	Yes = 1, No = 0, Unclear = 0	
21. Were main outcome measures used accurate? (valid and reliable)	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY-CONFOUNDING (SELECTION BIAS)	**Yes/No/Unclear**	**Score**
22. Were patients in different intervention groups recruited from the same population?	Yes = 1, No = 0, Unclear = 0	
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes = 1, No = 0, Unclear = 0	
24. Were study subjects randomized to intervention groups?	Yes = 1, No = 0, Unclear = 0	
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes = 1, No = 0, Unclear = 0	
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes = 1, No = 0, Unclear = 0	
27. Were losses of patients to follow-up taken into account?	Yes = 1, No = 0, Unclear = 0	
POWER	**Yes/No/Unclear**	**Score**
28. Was the study sufficiently powered to detect clinically important effects where probability value for a difference due	Yes = 1, No = 0, Unclear = 0	

Table 14: Downs and Black primary literature score summary

Article	Downs & Black Categories (item#)					Total
	Reporting (1-10)	External Validity (11-13)	Internal Validity Bias (14-20)	Internal Validity Confounding (21-26)	Power (1)	
Lian, 2014	11/11	2/3	7/7	4/6	1/1	25/28
Tokunago-Nakawatase, 2014	11/11	2/3	5/7	5/6	1/1	24/28
Long, 2014	11/11	3/3	5/7	4/6	0/1	23/28
Salas-Salvado, 2014	9/11	2/3	6/7	4/6	1/1	22/28
Hellgren, 2013	10/11	2/3	4/7	4/6	0/1	20/28

Data Extraction

The information contained in the "Review authors' assessment…" and "Main Findings" columns below include mainly direct quotations from the review articles included in our synthesis. The claims of primary study quality, the strengths and weaknesses of the review articles, and the evidence findings are those as stated by the review authors and have not been interpreted or altered by the CHRSP project team members.

Systematic Review Literature: Data Extraction

Key: Intervention Types

Mixed: Lifestyle/Drugs/Surgery
Lifestyle: Diet & PA
Lifestyle & Drug
Lifestyle: Diet Alone
Lifestyle: PA Alone
Screening & Lifestyle
Drug

Table 15: Systematic review evidence, data extraction

Citation, AMSTAR score, type & number of included studies	**Setting**	**Description of prevention programs/activities**	**Review authors' assessment of included study quality/review strengths & weaknesses**	**Main findings**
Aguiar, 2014 SR,MA **AMSTAR: 55%** 23 articles from 8 studies	2 USA, 1 New Zealand, 1 Austria, 1 Netherlands, 1 Australia, 1 Finland, 1 UK	Program: Lifestyle Diet and Exercise multi-component (**diet + aerobic exercise + resistance training**) lifestyle interventions Mode of Delivery "Five studies [33-40, 42-51] used an individual face-to-face mode as the primary means of intervention delivery,	Quality Assessment • Risk of bias (10-item quality checklist adapted from the Consolidated Standards of Reporting Trials (CONSORT) statement). "The 10-item scale and explanations of the scoring for each item	Weight Change: • "Seven of the eight studies reported a reduction in weight (kg) for the intervention group at the end of their respective interventions and four of the five RCTs reported significant weight loss for the intervention group compared to controls"(p.4). • "In total, 325 intervention and 290 control participants (total 644) from four studies were included [Lindstrom et al 2003; Maculey et al

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		while three studies [29-32, 41] used a group face-to-face mode. All studies conducted supervised individual and group exercise programs for some period of the intervention (Additional file 2). One study had an initial one-week period with a physical therapist and thereafter the exercise program was self-driven [32]. Most studies used gym facilities, however one study used an unsupervised home-based RT component for one of their intervention groups [41]" (p.3). Length of Program "Median intervention length was 12 months (range 4–48 months) with a follow-up of 18 months (range 6.5 - 48 months)" (p.3). Diet and Exercise prescription: "participants were advised to perform aerobic exercise for an average of 5.0 ± 1.5 days.wk^{-1} (mean ± SD), with an average duration of 157.5 ± 44.4 min.$^{wk-1}$ and to perform RT for an average of 2.3 ± 0.7 days.$^{wk-1}$ for an average duration of 90.0 ± 24.5 min.$^{wk-1}$. Five studies prescribed energy restriction for weight loss and seven studies prescribed a specific dietary macronutrient profile" (p.3).	are available (see Additional file 1). Each item was scored with a '1' for 'yes' or '0' for 'no'" (p.3). • three studies were classified as having a high risk of bias (score ≤ 5) [Burtshcer et al, 2009; Payne et al, 2008; Page et al1993/1992] (p.4) • **four studies as having a low risk of bias** (score ≥ 6)[Finnish DPS Lindstrom et al; McAugley et al, 2009; (SLIM)Roumen et al, 2008; Villareal et al, 2006 • "Study design and intervention components were heterogeneous amongst the included studies, which may account for some of the variation observed in the outcomes assessed" (p.4). Strengths:	2002; Roumen et al 2008; Villareal et al 2006]. The interventions were statistically heterogeneous ($\chi 2$ = 18.04, d.f. = 3, P < 0.001, I2 = 83%), so the random effects model was used. Meta-analysis (Figure 2) revealed a significant reduction in weight favoring the interventions over controls at the last reported assessment (WMD −3.79 kg [−6.13, -1.46; 95% CI], Z = 3.19, P = 0.001). The time frame of assessments varied from four to 36 months"(p.6). Glucose Intervention: • "FPG was reported in all eight studies (Additional file 3). Only two of the five RCTs reported significant differences between the intervention and control groups" (p.4). • "In total, 331 intervention and 307 control participants (total 667) from five studies were included [Lindstrom et al 2003; Maculey et al 2002; Page et al 1993; Roumen et al 2008; Villareal et al 2006]. The interventions were statistically homogenous ($\chi 2$ = 3.01, d.f. = 4, P = 0.56, I2 = 0%), so the fixed effects model was used. Meta-analysis (Figure 3) revealed a significant reduction in FPG favoring interventions over controls at the last"(p.6). Exercise Programs: "The reporting of exercise programs was inconsistent between studies and most studies provided only general descriptions of their exercise programs"(p.7).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		Comparator Usual Care (5/8 had a control group)	"This is the first review to synthesize the evidence of multi-component interventions including diet, aerobic exercise and RT for the prevention of type 2 diabetes. It adhered to the PRISMA statement for the reporting of systematic reviews and meta-analyses; a comprehensive search strategy was performed across multiple databases with no date restrictions; high agreement levels for quality assessments were achieved; and detailed data extraction was performed to allow for comparisons between studies"(p.8). Limitations: "Meta-analyses for weight and FPG were based on a small number of studies and the meta-analysis for weight was statistically heterogeneous. The sample for the meta-analyses consisted of 62% females, which introduces a sex bias.	T2DM incidence: "Of the studies reviewed, incidence of T2DM was only reported in the Finnish DPS and SLIM studies (up to 58% reduction in T2DM incidence) This finding is of great interest, particularly since the US DPP, which did not prescribe RT as part of their physical activity recommendations, also reported a 58% reduction in diabetes incidence (after 2.8 years) [5]. This suggests that multi-component T2DM prevention programs that include RT are effective, but whether RT provides benefits additional to dietary and aerobic components requires further investigation" (p.8). Successful Design Characteristics: "Design characteristics of studies that achieved significant changes for **weight loss and FPG** [29-31,33,36-39,41] included: face-to-face intervention delivery mode (individual and/or group), an average of eight contacts per month (including face to face sessions, emails and phone calls), and a minimum of six (preferably 12) months of follow up. **Lifestyle intervention characteristics** included: 150–210 minutes (3–5 sessions) of aerobic exercise per week; 60–120 minutes (1–3 sessions) of RT per week; recommendations for a specified macronutrient diet profile, energy restriction for weight loss and setting a weight loss goal of 5-10%"(p.8). Overall:

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			Furthermore the mean age of participants was 54.5 ± 9.7 years and only one study targeted older individuals (>65) [29-31]. This limits the generalizability of the results particularly for older individuals and highlights an evidence gap in the field. Regular resistance training may result in gains or maintenance of muscle mass; consequently weight loss as an outcome by itself would be confounded by the inability to discriminate between loss of fat mass and gains in fat free mass"(p.8).	"This systematic review found that multi-component lifestyle interventions incorporating diet + aerobic exercise + RT conducted in at risk or prediabetic adult populations were efficacious for inducing modest weight loss and eliciting small improvements in glycemic control, together with improvements in aerobic fitness and dietary intake. The impact of interventions on muscular fitness and physical activity were not consistently reported, making it difficult to determine the contributions of these components towards improvements in glucose regulation" (p.7). <u>Conclusions:</u> "Multi-component lifestyle interventions to prevent T2DM, which include a dietary intervention and both aerobic and resistance exercise training, are modestly effective in inducing weight loss, improving impaired fasting glucose, improving glucose tolerance and improving dietary and exercise outcomes in at risk and prediabetic adult populations. These results support the current exercise guidelines for the inclusion of RT in T2DM prevention" (p.9).
Dunkley, 2014 SR, MA AMSTAR: 64% 25 studies used for the SR (22/25 for the MA)	Primary Care, University based support centre, Community, outpatient, workplace USA 11 Australia 2 Finland 2	<u>Lifestyle</u>: "Lifestyle interventions aimed to translate evidence from previous efficacy trials of diabetes prevention into real world intervention programs"(p.922). "**dietary intervention or physical activity intervention or both**. Standard/ brief advice on diet and/or exercise was considered to be comparable with usual	<u>Quality Assessment:</u> • "U.K.'s National Institute for Health and Clinical Excellence (NICE) quality appraisal checklist for quantitative intervention studies. The checklist includes criteria for assessing the internal and external validity of	<u>Change in body composition (available from 24/25 studies):</u> • "For both NICE and IMAGE guidelines, respectively, greater adherence resulted in better outcomes for waist circumference (-0.52 cm, P = 0.007; -0.80 cm, P = 0.001) and triglycerides (-0.03 mmol/L, P = 0.016; -0.04 mmol/L, 0.023). For BMI, the improvements were only significant for adherence to NICE guidelines (-0.12 kg/m2, P =

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
	Netherlands 2 UK 2 1 Spain 1 Poland 1 Germany 1 Greece 1 Norway 1 Japan	care and not judged to be an active intervention" (p.924). "One study focused solely on the effectiveness of physical activity intervention (54), 1 combined dietary intervention and a supervised exercise program (44), and 23 considered the effectiveness of combined dietary and physical activity intervention"(p.924) <u>Follow up:</u> Length of follow-up ranged from 12 months on average (one study avg. was 4 years) Breakdown of interventions by study • effectiveness of PA (54) • combined dietary intervention and supervised exercise program (44) effectiveness of combined dietary and PA intervention (all others) <u>Comparator</u>: Usual Care/minimal health advice	experimental and observational quantitative studies (randomized controlled trials [RCTs], nonrandomized controlled trials, and before and after studies) and allows assignment of an overall quality grade (categories ++, +, or 2)."p924 • "Due to high levels of heterogeneity, we used random-effects models throughout to calculate effect sizes"p924 • 19/25 studies achieved high-quality grading for internal validity (p.925) • 11/25 studies achieved high-quality score for external validity (p.925) • "Overall, considerable heterogeneity was evident between studies in relation to several key characteristics including the setting, population, criteria used to identify diabetes risk,	0.028). There was no effect on any of the other outcomes" (p.930). • "The 22 translational diabetes prevention programs included in our [direct pairwise] meta-analysis significantly reduced weight in their intervention arms by a mean 2.3 kg [(95% -2.92 to -1.72; I^2 = 93.3%)] at 12 months of follow-up" (p.930). • "Adherence to guideline recommendations on intervention content and delivery was significantly associated with a greater weight loss such that, for each 1-point increase on the 12-point scale for adherence to NICE recommendations an additional 0.4 kg (P = 0.008) of weight loss was achieved; furthermore, for waist size a significant reduction of 0.5 cm was achieved for each point increase"(p.930). • "Our view is that, despite the drop-off in intervention effectiveness in translational studies, the level of weight loss found in our analysis is still likely to have a clinically meaningful effect on diabetes incidence"(p.930). • "The strong association between increased weight loss and increased adherence to guideline recommendations is of particular interest. Where complete data were available, the coefficients were larger: -0.52 kg per point increase (95% CI -0.95 to - 0.10) for adherence to NICE guidance on a 12-point scale and -0.77 kg per point increase (95% C-1.28 to -0.26) for adherence to IMAGE guidance on a 6-point scale. This may reflect a

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			interventions, and follow-up"(p.925). Strengths: "This study is novel in that it provides an updated meta-analysis of a global set of lifestyle interventions for diabetes prevention. Our study used comprehensive search criteria and focused on establishing the utility of pragmatic attempts to achieve diabetes prevention in real world service delivery settings. It also provides novel data that appear to validate the usefulness of recent guideline based recommendations on the content of lifestyle interventions for diabetes prevention"(p.930). Limitations: • "Outcome data on changes in the key lifestyle behavior targets (physical activity and diet) were poorly reported"(p.930).	reduction in the statistical noise caused by missing data, or it may reflect the fact that studies that had a stronger behavioral science input were more likely to report the intervention content in detail (and were also more likely to be effective). Overall, these data suggest that a high proportion of the variation in weight loss could be explained by variations in intervention design. The implication is that a design based on guideline recommendations should lead to performance at the higher end of the range (>4 kg)"(p.930). T2D Incidence: • Across the eight studies that reported incident diabetes, the pooled incidence rate was 34 cases per 1,000 person-years (95% CI 22–56), which gives the number needed to treat as 29"(p.930). Physical Activity and Diet Change: • "Outcome data for change in physical activity and diet were poorly reported" (p.925) • "few of the studies that we examined provided data on dietary intake or physical activity, so we cannot be sure whether diabetes prevention in these studies is driven by increased physical activity, dietary change, or both"(p.930) Other: • Where data were available, we found significant reductions in other diabetes and cardiovascular

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• "The study is limited in that there were insufficient data to analyze outcomes beyond 12 months; our findings may not translate into long-term therapeutic value due to uncertainty around sustaining outcomes, such as weight loss, in the longer term"(p.930). • "results in individual studies were not always reported on an intention-to-treat basis, leading to a likely overestimation of effect sizes. Assuming no change in weight for those with missing data, sensitivity analyses that we conducted suggest that weight loss could be up to 0.5 kg less in practice than the figures reported in the studies"(p.930). • "our analysis was restricted to intervention arms only; however,	risk factors, including blood glucose, BP, and some cholesterol measures"(p.930). • "For both NICE and IMAGE guidelines, respectively, greater adherence resulted in better outcomes for waist circumference (-0.52 cm, P = 0.007; -0.80 cm, P = 0.001) and triglycerides (-0.03 mmol/L, P = 0.016; -0.04 mmol/L, 0.023)"(p.930). <u>Conclusions</u>: "Our review suggests that pragmatic lifestyle interventions are effective at promoting weight loss and could potentially lead to a reduced risk of developing diabetes and cardiovascular disease in the future. However, the difficulties in translating this evidence into practice and in delivering guideline-based interventions need to be overcome. The ability to implement these findings in practice may be further hampered by a lack of resource for service provision, the design of efficient risk identification systems, and engagement of politicians and health care organizations in funding national diabetes prevention programs; diabetes prevention strategies require substantial up-front investment to accrue longer-term benefits (7)" (p.931). Overall, the interventions were effective, but there was wide variation in effectiveness. Adherence to international guidelines on intervention content and delivery explained much of the variance in effectiveness, implying that effectiveness could be improved by maximizing guideline adherence.

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			sensitivity analysis, restricted to RCTs only, indicated a mean weight change (-2.7 kg [95% CI -4.2 to -1.2]) that is similar to the overall result. These findings suggest that the estimate based on intervention arms only is likely to be robust" (p.931).	However, more research is needed to establish optimal strategies for maximizing both cost-effectiveness and longer-term maintenance of the lifestyle changes that these programs can achieve"(p.931).
Dunkley, 2012 SR, MA AMSTAR: 64% 13/16 RCTs for MA	6 USA 1 India 1 Iran 3 Italy 1 Norway 1 Greece 1 Netherlands 1 Europe/USA 1 UK	<u>Lifestyle: Diet, Exercise, Drug</u> "Study interventions (alone or in combination) included: (i) individualized/intensive dietary advice, (ii) supervised exercise sessions, (iii) exercise advice, (iv) metformin, (v) rosiglitazone, (vi) atorvastatin, (vii) pravastatin, (viii) lovastatin, (ix) fenofibrate, (x) sibutramine and (xi) rimonabant. Standard/brief advice on diet and/or exercise was considered to be comparable with usual care and not	<u>Quality Assessment:</u> • "We assessed the quality of selected studies according to several key indicators, which are known to influence the risk of bias in trials. The criteria included those recommended by the Centre for Reviews and Dissemination [18]" (p.617). • "Insufficient trials reported cardiovascular events/mortality, or incidence of type 2 diabetes, to conduct a meta-analysis for these outcomes" (p.617).	<u>Change in Metabolic Syndrome</u> • "Using random-effect models, both lifestyle (odds ratio, OR 3.81; 95% confidence interval, CI 2.47–5.88) and pharmacological interventions (OR 1.59; 95% CI 1.04–2.45) were statistically superior compared with control for reversing metabolic syndrome. Using mixed treatment comparison methods, the probability that lifestyle interventions were the most clinically effective was 87%." (p.616). • "Generally, the results indicate that lifestyle\ interventions are more effective at reversing metabolic syndrome than pharmacological therapies" (p.620). • "The direct pairwise meta-analysis on the grouped network shows that lifestyle interventions increase the odds of metabolic syndrome reversal by nearly fourfold (OR 3.81; 95% confidence interval, CI 2.47–5.88) and pharmacological

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		judged to be an active intervention"(p.618) • 7 = effectiveness of diet alone (2 diet alone, 2 exercise alone, 3 combined dieta and exercise) • 6 pharmacological interventions alone (4 lipid lowering, 1 antidiabetic, one antiobestity) • 3= lifestyle and pharmacological intervention <u>Length of follow</u>- up: ranged = 26weeks to 10yrs <u>Comparator:</u> "Standard/brief advice on diet and/or exercise was considered to be comparable with usual care and not judged to be an active intervention"(p.618)	• "Overall, considerable heterogeneity was evident between studies in relation to several key characteristics including the setting, population, interventions and follow-up" (p.620). • "All studies adequately reported their eligibility criteria, and the majority provided a measure of variability for their primary outcome (14/16) and analysed data on an intention-to-treat basis (13/16).However, randomization methods and allocation concealment were more poorly reported. Generally, studies investigating lifestyle interventions tended to achieve lower scores because of the impossibility of blinding participants and care providers" (p.620). <u>Strengths: p.622</u>	interventions by 60% (OR 1.59; 95% CI 1.04–2.45), compared with control, with moderate levels of statistical heterogeneity (Table 3). Publication bias was assessed for the lifestyle versus control comparison only; no significant publication bias was seen (p = 0.84, figure S2). The number of trials for other comparisons was too few to enable publication bias to be assessed. The mixed treatment comparison results indicated that lifestyle had the largest probability (87.4%) of being the best intervention" (p.620). • "The direct-pairwise results for the full network indicate that antidiabetic drugs, diet, exercise and diet and exercise combined all increased the odds of metabolic syndrome reversal compared with control (Table 3 and figure S3). However, a high level of statistical heterogeneity was seen for the antidiabetic drug versus control comparison (I^2 = 78.4%). The results of the mixed treatment comparison analysis showed similar results to the pairwise analysis (Table 3). Diet and exercise (33.8%), antiobesity drugs with lifestyle advice (31.4%) and diet alone (17.5%) had the largest probabilities of being the best interventions" (p.620). • "the mixed treatment comparison results generally agreed with those from the direct analysis but tended to be more conservative. All the mixed treatment comparison results except one fell within the 95% CI of the direct estimates, giving a high level of consistency. The two mixed

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			• No previously published SR and MA of the evidence regarding interventions aimed at reversing metabolic syndrome • Robust methods used, including strategies for obtaining all relevant outcome data that were available to study authors even when not reported <u>Limitations: p. 622</u> • Considerable clinical heterogeneity between the interventions • Differences between populations, follow-up period and treatment of control group subjects hinder comparisons • Trials may have achieved higher levels of compliance among participants than would be the case in routine practice • Pharmacological interventions identified	treatment comparison models had an acceptable level of fit, with the residual deviance being roughly equal to the number of unconstrained data points in both cases" (p.620). • "Our meta-analysis of 13 studies including 3907 participants with metabolic syndrome indicates the benefits of both lifestyle and pharmacological interventions to reverse metabolic syndrome. Lifestyle interventions appear to be the most effective; however, the trials were too heterogeneous to be able to make firm conclusions about which aspects of lifestyle interventions, at a detailed level, are most effective. Insufficient trials reported cardiovascular disease events or incidence of type 2 diabetes to enable a meta-analysis to be conducted on these outcomes" (p.621). <u>Change in T2D incidence and Cardiovascular events and mortality:</u> • "Insufficient trials reported cardiovascular disease events or incidence of type 2 diabetes to enable a meta-analysis to be conducted on these outcomes" (p.621). • "Subgroup analyses of people with metabolic syndrome from three large trials of statin therapy [Geluk, 2005; Clearfield, 2005; Sattar, 2003] found that treatment reduced cardiovascular mortality and morbidity after follow-up periods ranging from 4 to 10 years. However, treatment effects

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			several different types of therapies some of which were suspended at the time of the review for use in routine clinical practice following concerns over adverse effects (rimonabant, sibutramine, rosiglitazone) • "Highest levels of statistical heterogeneity were seen for the comparisons, which included the fewest number of studies"(p.622) • Insufficient trials reported on long-term clinical outcomes so focused on reversal of metabolic syndrome as primary outcome. • "Additionally, reversal of metabolic syndrome could represent anything from significant amelioration of several metabolic abnormalities to only slight improvement of one	were statistically significant in only two of the trials [Geluk, 2005; Clearfield, 2005]" (p.620). <u>Conclusions:</u> "Our meta-analysis shows that interventions aimed at promoting lifestyle changes are effective for reversing metabolic syndrome and reducing cardiovascular and diabetes risk factors. However, there is lack of data on compliance. Further evidence is also needed to explore if these benefits are sustained and translate into longer term improvements in health outcomes, including primary prevention of diabetes and/or cardiovascular disease. The effectiveness of pharmacotherapy for reversing metabolic syndrome was also shown, but there is currently a lack of data on safety and cost-effectiveness in this patient group. Additionally, healthcare professionals may not support widespread prescribing for what some perceive to be a disorder of lifestyle" (p.623).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			component of the syndrome" (p.622). • "use of dichotomous cut-points rather than continuous values, for individual components, does not allow for consideration of the magnitude of risk"(p.622). • "variation in the overall quality of included studies"(p.622) • "In general, allocation concealment was poorly reported and this has been linked to an increased likelihood of reporting significant findings" (p.622). • "studies investigating lifestyle interventions tended to achieve lower quality scores because of the difficulty of blinding participants and care providers" (p.622) • "although the potential benefit of interventions included within this review is clear, much of	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			the evidence came from subgroup analyses. Most of these analyses were not specified in advance; consequently, the findings should be interpreted with caution" (p.622)	
Everson-Hock, 2013 SR AMSTAR: 45% 35 total (12 quantitative intervention, 23 qualitative studies)	Community, focus on UK	Lifestyle: • "…community-based **physical activity and dietary interventions**"(p.266) • "Quantitative intervention studies were categorised as: dietary/ nutritional; food retail; physical activity; and multi component interventions" (p.267) • Qualitative: Barriers and facilitators of lifestyle change Follow-up: not reported Comparator: Usual care, placebo/attention or no comparison	Quality Assessment: • "Quality assessment of quantitative and qualitative studies was undertaken using the appropriate National Institute for Health and Clinical Excellence (NICE) quality assessment checklists (NICE, 2009). Each study was rated as++, + or − on the basis of characteristics such as sampling, measurement, analysis and internal and external validity of findings (Supplementary Tables 2 and 3)" (p.266) • "Two quantitative intervention studies were rated ++, eight were rated + and two were rated −. The main	**Quantitative Findings** Diet and Exercise: • Choose and cook healthy food: "There was evidence of mixed effectiveness on fruit and vegetable intake, consumption of high fat food, physiological measurements and nutrition knowledge. Evidence suggested no significant impact on weight control or other eating habits, such as intake of starchy foods, fish or fibre."[(Ashfield-Watt et al., 2007+; Bremner et al., 2006+);(Kennedy et al., 1998−; McKellar et al., 2007+; Steptoe et al., 2003++; Wrieden et al., 2007+)] (p.267). • Introduction of large scale food retailing outfit in intervention area: "Both studies indicated mixed effectiveness on fruit and vegetable intake, and evidence suggested no significant impact on health outcomes. Neither study identified a negative impact on any outcome" [(Cummins et al., 2005+; Wrigley et al., 2003−)] (p.267). • Physical Activity: "Overall, physical activity interventions showed mixed effectiveness"; "No studies identified a negative impact on any outcome" (p.268).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			limitations to quality were poor description of the source population, lack of sufficient power or power calculations and lack of reported effect sizes (Supplementary Table 2). Eight qualitative studies were rated ++, 18 were rated + and none were rated −. The main quality limitations were reporting of participant characteristics and researcher/participant interaction, as well as data collection and analysis methods (Supplementary Table 3)" (p.267). <u>Limitations:</u> • "Study quality was variable, with only two intervention studies being rated as high quality, one of which was only two weeks in duration" (p.270).	**Qualitative findings** <u>Facilitators (+) and Barriers (-) for implementation/participation of interventions (p268-270)</u> 1) **Resources**: • (+)continuous funding from a large award, developed action plan to target funding and labour effectively • (-) lack of funding, time and labour for running interventions, lack of available facilities for preparing, storing and transporting food (Bremner et al., 2006+; Dobson et al., 2000+; Kennedy et al., 1998+) 1) **Awareness** of intervention: • (+) word of mouth being most successful strategy (Dobson et al., 2000+; Withall et al., 2009+) 2) **Acceptability** of intervention: • (+) positive attributes of health workers including knowledge of the community, facilitating empowerment, engaging participants in the subject matter, communicating info in a meaningful way, empathy and trustworthiness (Dobson et al., 2000+; Gray et al., 2009+; Kennedy et al., 1998+; Kennedy et al., 1999+; Peerbhoy et al., 2008+; Spence and van Teijlingen, 2005+; Wormald et al., 2006+). • (+) Women only classes, activities on the weekend, free sessions, child-care and food,

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• "Behavioural outcomes of interventions were mainly self-reported, therefore some caution is required in interpreting our quantitative review findings. Since no study reported longer-term health outcomes, it is impossible to directly assess the impact of the interventions on the health of those in low-SES groups" (p.270). • "Trial participants are less likely to be male, current smokers or within the lowest quartile of SES than non-participants or defaulters (Chinn et al., 2006; Waters et al., 2011). Thus, our quantitative review findings may not necessarily be representative of the hardest-to-reach low-SES groups" (p.270). <u>Strengths:</u>	tailored recipes and enjoyable activities, social inclusion (Dobson et al., 2000; Gray et al., 2009+; Lindsay et al., 2008+; Peerbhoy et al., 2008+; Rankin et al., 2006++; Rankin et al., 2009++; Thomson et al., 2003+). • (-) image associated with certain health promotion activities (Coleman et al., 2008++; Rankin et al., 2006++; Stead et al., 2004+) 3) **Delivery** of intervention and content • (+) through practical demonstrations, progressive small steps towards change, male-only classes and orientation to weight management, delivering content according to participants' needs, incentives such as free food, using familiar and affordable food and using community members to deliver the intervention (Dobson et al., 2000+; Gray et al., 2009+; Kennedy et al., 1998+; Peerbhoy et al., 2008+; Rankin et al., 2006++; Spence and van Teijlingen, 2005+; Stead et al., 2004+;Wormald et al., 2006+) <u>Facilitators (+) and Barriers (-) to behavioral change (p268 -270)</u> 1) Information **Source/Availability** • (+) television when used to improve knowledge of food and nutrition (Daborn et al., 2005+; Dibsdall et al., 2002++; Gough and Conner, 2006++;Wood et al., 2010+) 2) **Understanding** of health message

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			"A strength of this review was the inclusion of many types of evidence, which allowed us to explore effectiveness findings in contextual detail and create explicit links between quantitative and qualitative evidence, using methods appropriate for the data (Harden and Thomas, 2007; Kavanagh et al., 2012). This enabled us to identify gaps in the intervention evidence base and thus directions for future research (Harden and Thomas, 2007)"(p.270).	• (-) inhibitory when people felt bombarded with info (Daborn et al., 2005+; Dibsdall et al., 2002++; Gough and Conner, 2006++;Wood et al., 2010+) • (-) a lack of clear information, misunderstanding of food messages and the perception of healthy eating messages as complex, especially sugar content and the classification of fats, a balanced diet (misinterpreted as a balance of 'good' and 'bad' foods) and the '5-a-day' message (misinterpreted as five portions of fruit) (Gray et al., 2009+; Lawrence et al., 2009+; Stead et al., 2004+; Wardle et al., 2001+; Wood et al., 2010+). 3) Existing **Health attitudes** • (-)lack of perceived control over weight, no clear perceived links between lack of exercise and chronic conditions, and food and health, belief that it isn't good to be 'too healthy' (Dibsdall et al., 2002++; Lawrence et al., 2009+; Nic Gabhainn et al., 1999+; Whelan et al., 2002+; Withall et al., 2009+; Wood et al., 2010+) 4) **Perceived capabilitie**s • (-) poor initial level of fitness, perceived lack of sporting capability, cooking skills and confidence in cooking meals from scratch • (+) confidence in cooking and experimenting with food (Coleman et al., 2008++; Lawrence

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				et al., 2009+; Peerbhoy et al., 2008+; Stead et al., 2004+) 5) **Current Lifestyl**e • (-) commitments and responsibilities, stress, comfort eating, being stuck in a rut, embarrassment, belief that activity around the home is sufficient, lack of time, boredom (for unhealthy eating) (Gough and Conner, 2006++; Lawrence et al., 2009+; Nic Gabhainn et al., 1999+; Price, 2007+; Whelan et al., 2002+; Withall et al., 2009+) 6) **Affordabilit**y • (-) cost of buying healthy food, perceived lack of affordable local food, public transport costs, cost of cooking multiple meals for different preferences, marketing strategies promoting unhealthy foods and wasting money buying food that the family would not eat, cost of physical activity transport and facilities (Dibsdall et al., 2002++; Kennedy et al., 1998+; Lawrence et al., 2009+; Parry et al., 2007+; Peerbhoy et al., 2008+; Price, 2007+; Whelan et al., 2002+; Withall et al., 2009+) 7) **Environmental** Factors • (-)Perceived lack of local shopping amenities and accessing shops with children could be prohibitive to healthy eating, fear of crime, intimidation and attack, dark evenings and poor weather were barriers to outdoor physical activity (Cavill and Watkins, 2007++;

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				Lawrence et al., 2009+; Parry et al., 2007+; Peerbhoy et al., 2008+) 8) Social **Norms** • (-) heathy food seen as boring and unsatisfying, prioritizing traditional food and family preferences over healthy choices, perceived lack of family support in childhood, parental influence, habit in unhealthy shopping and eating and living alone. Women's eating practices were often influenced by a perceived lack of personal control and importance. Men's barriers centred on personal preferences (to be overweight rather than 'thin'), personal choice and good current health. • (+) women's motivation to cook healthy food for their children and men's motivation to engage in 'masculine' physical activity to compensate for an unhealthy diet (Daborn et al., 2005++; Dibsdall et al., 2002++; Gough and Conner, 2006++; Gray et al., 2009+; Kennedy et al., 1998+; Lawrence et al., 2009+; Peerbhoy et al., 2008+; Stead et al., 2004+; Whelan et al., 2002+; Withall et al., 2009+; Wood et al., 2010+; Wormald et al., 2006+) <u>Conclusions:</u> • Overall, some dietary and physical activity interventions appeared to be effective and acceptable among low SES groups in the UK, although others demonstrated little or no impact.

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				There was mixed evidence of effectiveness across all categories of intervention. While no intervention demonstrated a clear positive effect on all outcome measures considered, some studies showed positive impacts on some outcomes and no intervention had a negative impact on any outcome" (p.270). • "Sufficient resources are needed to deliver meaningful interventions. Key workers delivering interventions need knowledge and understanding of the community; possibly be a community member. Interventions can increase acceptability by using enjoyable, creative and innovative activities and enhancing (and harnessing) social inclusion. Negative or misunderstood beliefs and connotations surrounding healthy eating and physical activity need to be addressed. Clear and consistent information on healthy eating and physical activity is needed, encompassing advice provided by the government, on TV and in interventions. Interventions could enhance people's control beliefs and self-confidence in their ability to cook and eat healthily and be physically active, and correspondingly address the role of the whole family in lifestyle choices. The affordability and perceived affordability of healthy lifestyle choices need to be improved, and these could be complemented with education on budgeting. Existing motivators could be harnessed within interventions, such as cooking

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				healthy food to improve children's health or exercising to bolster masculinity" (p.270). • "Overall, evidence on the effectiveness of community-based dietary and physical activity interventions is inconclusive" (p.270).
Geng, Liang, 2013 MA AMSTAR: 45% 9 RCTs	Data from trials	**Drug** class: angiotensin converting enzyme inhibitors Follow up: ALLHAT – mean 4.9 years ANBP2 – median 4.1 years CAPPP – mean 6.1 years STOP-2 – 2.3 years PEACE – median 4.8 years EUROPA – mean 4.3 years HOPE – mean 4.5 years SOLVD – median 2.9 years DREAM – median 3 years <u>Comparator:</u> Placebo or non-ACEI drugs	<u>Quality Assessment</u>: "Methodological quality of included RCTs was assessed by several domains: randomization; allocation concealment; blinding of investigators, participants, and outcome assessors; completeness of follow-up; description of withdrawals; and application of intention-to-treat analysis" (p.2606). <u>Limitations:</u> • "incidence of new-onset diabetes at the end of follow-up was extracted from the trials with different follow-up periods, so the incidence of new-onset diabetes varied greatly among the trials" (p.2608). • "due to different ages of these trials, diabetes was defined differently	Angiotensin converting enzyme inhibitors (ACEIs) <u>T2D incidence:</u> • "Overall, there were 2325 new cases of T2DM (2325/30,228, 7.7%) in the ACEIs group compared with 3933 new cases (3933/41,900, 9.4%) in the control group [OR 0.80, 95%CI 0.71–0.90, P=0.0003]. Compared with the control group, incidence of new-onset diabetes was significantly reduced in the ACEIs group, irrespective of achieved blood pressure (BP) levels [ACEIs with lower achieved BP, OR 0.82, (0.69, 0.97); ACEIs with higher achieved BP, OR 0.79, (0.64, 0.98)]. ACEIs therapy was associated with a significant reduction in the risk of new-onset diabetes compared with beta-blocker/diuretics [OR 0.78, (0.65, 0.93)], placebo [OR 0.79, (0.64, 0.96)], or CCBs [OR 0.85, (0.73, 0.99)] (Fig. 1). ACEIs treatment was associated with a significant reduction in the risk of new-onset diabetes in patients with hypertension [OR 0.80, (0.68, 0.93)], CAD or cardiovascular disease [OR 0.83, (0.68, 1.00)], or heart failure [OR 0.22, (0.10, 0.47)] (Fig. 2). Among patients with IGT or IFG, ramipril did not significantly reduce the incidence of diabetes

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			among the trials. It could add clinical heterogeneity to this study" (p.2608). • "most participants recruited in these trials were white population and the information about other races was unavailable" (p.2608). • "according to the protocol of some trials, diuretics were added to the participants in the ACEI group with target BP unachieved under the monotherapy of ACEIs. It led to underestimate the beneficial effects of ACEIs on the incidence of new-onset diabetes" (p.2608) • "new-onset diabetes was not a prespecified outcome of the trial, nor was it confirmed by systematic glucose measurement, especially regular oral glucose tolerance test (OGTT). It is reported that without	[OR 0.91, (0.79, 1.05)], but significantly increased regression to normoglycemia" (p.2606). <u>Conclusions:</u> • "This meta-analysis indicated that ACEIs overall have beneficial effects on the prevention of new-onset diabetes, irrespective of achieved BP levels. ACEIs appear superior to beta-blockers/diuretics, placebo or CCBs for prevention of new-onset diabetes. ACEIs treatment was associated with significant reduced risk of new-onset diabetes in patients with hypertension, CAD or cardiovascular disease, or heart failure. Among patients with IGT or IFG, ramipril did not significantly reduce the incidence of diabetes, but significantly increased regression to normoglycemia. In this study, it has demonstrated that ACEIs treatment was associated with significant reduced risk of new-onset diabetes in patients with hypertension, CAD or cardiovascular disease, or heart failure. It suggests that ACEIs could provide additional benefits of lowering the risk of new-onset diabetes in patients with hypertension, CAD or other cardiovascular disease. To be noted, there are conflicting results in patients with CAD among the relevant three trials [9,11,12] though the participants recruited in these 3 trials had large similar characteristics" (p.2606). • "ACEIs have beneficial effects in preventing new-onset diabetes. ACEIs provide additional benefits of lowering the risk of new-onset diabetes in

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			OGTT, approximately one fifth of all cases of type 2 diabetes were undiagnosed [2]" (p.2609)	patients with hypertension, CAD or other cardiovascular disease" (p.2609).
Geng, 2012 MA AMSTAR: 36% 11 RCTs	Data from trials	**Drug**: angiotensin receptor blockers (ARBs) Less than 5yrs follow up Follow up: CASE-J – 3.2years HIJ-CREATE – Median 4.2 years SCOPE – 3.7 years CHAM-Alternative – Median 2.8 years CHAM-Preserved – Median 3.1 years KYOTO – median 3.27 PRoFESS – 2.5 years TRANSCEND – median 4.7 years VALUE – 4.2 years NAVIGATOR – median 5 years LIFE – 4.8 years <u>Comparators:</u> Placebo or Non-ARB drugs	<u>Quality Assessment</u>: "Methodological quality of included randomized controlled trials was assessed by several domains: randomization; allocation concealment; blinding of investigators, participants, and outcome assessors; use of intention-to-treat analysis; and completeness of follow-up" (p.236). <u>Limitations</u>: • "One limitation of this meta-analysis is that the data of new-onset diabetes rates were extracted from trials of different durations. Second, due to different ages of these trials, diabetes was defined differently among the trials. It could add clinical heterogeneity to this	Angiotensin receptor blockers (ARBs) <u>Incidence of new onset diabetes</u> • "Compared with control group, incidence of new-onset diabetes was significantly reduced in ARBs group [OR 0.79, (0.74, 0.84)] and various categories of ARBs subgroup. ARBs were associated with significant reduction in the risk of new-onset diabetes compared with placebo [OR 0.83, (0.78, 0.89)], beta-blocker [OR 0.73, (0.62, 0.87)], calcium channel blocker [OR 0.76, (0.68, 0.85)] and non-ARB [OR 0.57, (0.36, 0.91)]. ARBs were associated with significant reduction in the risk of new-onset diabetes in patients with hypertension [OR 0.74, (0.68, 0.81)], heart failure [OR 0.70, (0.50, 0.96)], impaired glucose tolerance [OR 0.85, (0.78, 0.92)] or cardio cerebrovascular diseases [OR 0.84, (0.72, 0.97)]. Compared with control group, incidence of new-onset diabetes was significantly reduced in ARBs group, irrespective of achieved blood pressure level. ARBs were associated with a lower incidence of new-onset diabetes in Western population [OR 0.81, (0.76, 0.85)] and Japanese population [OR 0.61, (0.48, 0.79)]."p236

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			study. Third, in most of the studies included, however, the incidence of diabetes was not the primary outcome of the trial, nor was it confirmed by systematic glucose measurement, especially regular oral glucose tolerance test (OGTT). It is reported that without OGTT, approximately one fifth of all cases of type 2 diabetes were undiagnosed [2]" (p.241).	• "This meta-analysis indicated that ARBs overall and various categories of ARBs have beneficial effect on the prevention of new-onset diabetes, irrespective of achieved BP levels. ARBs have beneficial effect on new-onset diabetes not only in hypertensive patients but also in patients with heart failure, cardio cerebrovascular diseases or IGT with cardiovascular disease or risk factors. In addition, ARBs appear superior to CCB, non-ARB, placebo or beta-blocker for prevention of new-onset diabetes. ARBs could lower the risk of new-onset diabetes in both Western population and Japanese population" (p.239). <u>Conclusions:</u> • "In this study, it has been demonstrated that ARBs could reduce the incidence of new-onset diabetes in patients with hypertension, heart failure, cardiocerebrovascular diseases or IGT with cardiovascular disease or risk factors. It suggests that ARBs might be used in not only hypertensive patients but also other patients with high risk of developing diabetes" (p.241). • "There is sufficient evidence that ARBs have beneficial effect in preventing new-onset type 2 diabetes. ARBs should be considered in patients with high risk of developing diabetes" (p.241).
Gillett, 2012 HTA AMSTAR: 82%	China, Finland, India, USA, Japan,	<u>Lifestyle:</u> The following interventions, either alone or in combination, are considered: • weight loss	<u>Quality assessment:</u> To assess the quality of the RCTs, the following criteria were used:	<u>Progression to diabetes</u>: • "In people with IGT, dietary change to ensure weight loss, coupled with physical activity, is

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
9 RCTs	the Netherlands, UK	• exercise • qualitative changes in diet. Wide range of follow-up <u>Comparator:</u> Standard treatment. Non-intensive lifestyle treatment.	1. method and description of randomisation 2. description of attrition/losses to follow-up 3. specification of eligibility criteria 4. blinding 5. power calculation 6. robustness of outcome measurements 7. similarity of group participants at baseline 8. data analysis. Overall study quality was rated as follows: A (all quality criteria met), B (one or more of the quality criteria only partially met) or C (one or more criteria not met). "Participants in the RCTs were volunteers and their results may have been better than in general populations. Even among the volunteers, many did not adhere. Some studies were not long enough to show whether the interventions reduced cardiovascular mortality as well as diabetes. The main	clinically effective and cost-effective in reducing progression to diabetes" (p.iv). • "Most of the studies show that progression to diabetes can be reduced, and regression to NGT increased" (p.68). • "There was also a tendency for the benefits to be lost not long after the intervention ended, with, for example, regain of weight. The exception was the DPS, 183 where benefit was largely maintained for 3 years after intervention ended. Perhaps a 4-year intervention can permanently improve lifestyle change, whereas short intervention does not. However, as noted above, studies with the longest follow-up show disappointing results in terms of CVD. The benefits of the lifestyle intervention were greatest in those with the highest compliance and who achieved more of the targets (such as weight loss and dietary change). For example, in the Finnish study, 183 those who achieved four or five of the five targets had a risk of developing diabetes which was only 23% of those who achieved none. However, even among the volunteers in the trials, many did not succeed and others succeeded in the short term (such as the first 6 months) but not in the longer term. The key to success is sustained lifestyle change, especially weight loss. In conclusion, lifestyle measures can be highly effective in reducing progression to diabetes but adherence to lifestyle change is the most important factor"(p.69).

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			problem is that we know what people should do to reduce progression, but not how to persuade most to do it" (p.iv). "A number of issues should be considered when assessing the validity of the trials and their outcomes, particularly in terms of generalisability to the UK population: • Trials were conducted in populations across the world (China, Finland, India, USA, Japan, the Netherlands, UK); as such, genetic and cultural variation may potentially confound the results. Progression rates varied considerably, with 80% of the intervention group in the Chinese trial (Da Qing190) progressing to diabetes. • Trials recruited participants using different criteria for IGT, different age ranges, sex	• **"There is consistent evidence from the trials, such as the DPP108 and DPS,183 that lifestyle measures – weight loss and physical activity – can reduce the development of diabetes in those with IGT. The results are best in those who achieve more of the goals. Lifestyle intervention in those who adhere is also highly cost-effective.** • It may be worth distinguishing between physical activity and exercise, with the former term referring to activities, such as walking, that can beincorporated into daily life and the latter referring to activities that require, for example, going to gyms or participating in sports. • The main problem is adherence. (Adherence is now preferred to the older term 'compliance' because it is supposed to have connotations of partnership and concordance, rather than'following doctor's orders'.337) • Some ethnic groups, such as South Asians, are more at risk of diabetes, and may get it earlier in life and at lower BMI levels. Cultural influences may make lifestyle changes more difficult, especially among women. • A review of previous economic modelling of prevention of diabetes showed that most studies conclude that is it cost-effective, with one prominent outlier. Uncertainties include the duration of the asymptomatic period between onset of diabetes and development of clinical diabetes, the rate of progression and whether it is

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			and BMIs. Self-selection (and therefore an increased likelihood of compliance) may have occurred with some recruitment methods. • Not all studies were powered or designed to look at progression to diabetes. • Duration of intervention and duration of follow-up varied between trials. • Some lifestyle interventions were individualised whereas others were conducted in groups and the number of intervention contacts, for example with dietitian, varied between trials. • Physical activity advice varied from recommended participation in light exercise once a day to several supervised sessions of moderate activity every week.	linear, and whether the risk is constant over lifetime, or whether those who are going to become diabetic do so within 10 years or so. It is worth noting that fewer than half of people with 'pre-diabetes' go on to develop diabetes. • Analysis of GPRD data showed that there appears to be little current activity in detection of, and intervention in, IGT, so any national programme would have to start from a low baseline. • Our modelling suggested that lifestyle intervention, when continued in those who respond during the first year, is highly cost-effective. This remains the case under a range of sensitivity analyses. • In those who do not lose weight and increase physical activity, a strategy of switching to metformin after 12 months is cost-effective. • A common finding in most lifestyle intervention studies is that good initial effects are not sustained over the long term, especially after the intervention ends. However, the Finnish DPS183 has produced 7-year results, 3 years after the end of the intervention period, showing persisting benefit. Perhaps an intervention that lasts for several years is required to produce a permanent change in lifestyle" (p.127). "**The pressure to introduce screening for undiagnosed T2DM is growing. However, were we to screen for diabetes, we would, depending on choice of test and cut-off levels used, identify more, or far more, people**

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• Dietary intervention ranged from recommendations to eat more fruit and vegetables to specific guidelines on recommended daily amounts of nutrients. • Subjective self-reported measurements of dietary intake and physical activity adherence are known to be unreliable. • Analysis was not on an ITT basis and because more subjects in the control groups developed diabetes and were withdrawn from study for treatment this may confound the results"(p.128).	**with IGT than with diabetes**. **This review was commissioned in response to the identification of that problem in our previous review of screening for diabetes**. Our remit was limited to non-pharmacological interventions. There is a strong body of evidence that there are effective ways of reducing progression to diabetes in people with IGT by lifestyle interventions, and these are likely to be considered cost effective. Progression to diabetes could be reduced by about half, if the results in the volunteers in trials such as DPP and DPS can be reproduced in routine care. However, adherence tends to be poor. The benefits of the lifestyle intervention were greatest in those with the highest compliance and who achieved more of the targets (such as weight loss and dietary change). For example, in the Finnish study,183 those who achieved four or five of the five targets had a risk of developing diabetes which was only 23% of those who achieved none. Weight loss is the most important goal. Furthermore, even among the volunteers in the trials, many did not succeed, and others succeeded in the short term (such as the first 6 months) but not in the longer term. The key to success is sustained lifestyle change, especially weight loss. We know what people need to do to reduce their risk of progression to diabetes, but not how to motivate them to do so" (p.138).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
Grant, 2009 Cochrane Review AMSTAR: 100% 16 RCTs	China, Japan Mostly conducted through Out-patients in Hospitals or clinics, with one taking place with inpatients	<u>Herbal medicine plus lifestyle modification:</u> • 15 Chinese **herbal medicines** "In the 16 studies lasting four weeks to two years there were eight different comparisons, with 15 unique herbal formulations investigated" (p.20) <u>Follow up range:</u> 28 days – 2 years <u>Breakdown</u> • nine trials compared nine Chinese herbal medicines with lifestyle modification as a control and co-intervention (*Jiangtang bushen* decoction (Fan GJ 2004), *Jinqi jiangtang* pills (Zhou DY 2003), *Liu wei di huang wan* pills (Zeng YH 2006), *Qimai jiangtang yin* decoction (Li CP 2004), *Tang kang yin* decoction (Yang B 2004), *Tang Heng I (*Yao Z 2001), *Xiaoke huayu* tablets (Hao AZ 2004), *Xiaoke yuye* decoction (Wei AS 2001) and *Jian pi zhi shen huo xue* (Tang QZ 2007); • two trials compared Chinese herbal formulas with a placebo with lifestyle modification as a co-intervention: *Bofu-tsusho-san* (Hioki C 2004) and *Dan zhi jiang tang jiao* (Fang ZH 2007); • one trial compared Qiwei	<u>Quality Assessment:</u> • "Most published reports of trials were lacking in details of trial Methodology"(p.10). • "Two authors independently assessed the risk of bias of each of the included studies against key criteria: random sequence generation; allocation concealment; blinding of participants, outcome assessors and intervention providers; incomplete outcome data; selective outcome reporting; and other sources of bias. Studies that did not adequately meet these criteria were considered at high risk of bias" (p.11). • "There were no outcome data in any of the trials on death from any cause, morbidity, diabetes complications, or costs. No serious adverse events or hypoglycaemic	<u>Blood glucose level/control:</u> • "In four of the nine trials, the Chinese herbal medicines combined with lifestyle modification were significantly better at reducing fasting blood glucose levels than lifestyle modification alone" (p.18). • "Six of the nine trials in this comparison reported significantly better results for reducing 2hr fasting blood glucose levels than the lifestyle modification control" (p.18). • "In this systematic review we found evidence from eight trials that Chinese herbal medicines combined with lifestyle modification were significantly better at normalising blood glucose levels then lifestyle modification alone (RR 2.07; 95% CI 1.52 to 2.82)" (p.20). <u>Glycosylated haemoglobin A1c</u> • 3 studies reported herbal medicines combined with lifestyle modification were all statistically significant in reducing HbA1c compared to the control of lifestyle modification alone. No meta-analysis was conducted to considerable statistical heterogeneity ($I^2 = 88\%$) Insulin • "In the six trials that measured insulin levels, significantly lower levels were detected in those taking Jiangtang bushen decoction (FanGJ 2004),Qimai jiangtang decoction (Li CP 2004), and Jinqi jiangtang tablets (Zhou DY 2003). No

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		tangping capsules with a placebo (Wang BQ 2008); • one trial compared Tang ping san with metformin, with a lifestyle modification as co-intervention (Qu LX 2002); • one trial compared Fufang cangzhu decoction with metformin (Shi J 2005); • one trial compared Jian pi zhi shen huo xue with acarbose (Tang QZ 2007); • one trial compared Yi qi yang yin huo xue combined with an antihypertensive medication with an antihypertensive medication alone (Lu X 2005); one trial compared Jinqi jiangtang pills with a basic education on IGT as a co-intervention and as a control (Wang YX 2005)." <u>Comparators:</u> • placebo; • no treatment; • pharmacological compounds (for example biguanides such as metformin, sulphonylureas); • non-pharmacological interventions (for example diet, exercise)	episodes were reported. We were only able to perform meta-analyses on two outcomes in this review and these should be interpreted cautiously. This is mainly due to issues of heterogeneity and because none of the specific herbal medicines comparison data was available from more than one study" (p.14). • The insufficient number of trials prohibited us from performing meaningful sensitivity analyses to clarify robustness of the review results to the exclusion of trials with inadequate methodology" (p.25). <u>Limitations:</u> • "Overall the positive evidence in favour of Chinese herbal medicines for the treatment of impaired glucose tolerance is	significant differences in insulin levels were found in those participants taking Tang Kang Yin (Yang B 2004) and Tang Heng I decoction (Yao Z 2001) compared with the lifestyle modification control group" (p.22). <u>T2D incidence (10 studies):</u> • "In a meta-analysis of eight trials, those receiving Chinese herbs were also more likely to have a reduced incidence of diabetes (RR 0.33; 95% CI 0.19 to 0.58). In the pooling of the results for the meta-analyses of the two measures of normalising blood glucose and incidence of diabetes there was no considerable statistical heterogeneity among the comparisons (I2 = 66% and I2 = 0%, respectively). It is important to note that there is a clinical difference in the herbal composition of these interventions and likely a difference in the active components. But these Chinese herbal medicines are not completely dissimilar" (p.20). • "There was no significant difference between *Jian pi zhi shen huo xue* (Tang QZ 2007) compared to acarbose, with both groups receiving lifestyle modification, on any of the outcome measures" (p.24). <u>Reduction of Cholesterol an triglcerides</u> • "Some of the Chinese herbal medicines showed potential for improving cholesterol and triglycerides along with normalising FBG. *Jian pi zhi shen huo xue, Jiangtang bushen*

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		Co-interventions were allowed as long as all arms of the randomised trial received the same co intervention(s). Only interventions performed for a minimum duration of four weeks were included" (p.4)	constrained by the following factors: a lack of trials that tested the same medicine, lack of details on co-interventions, unclear methods of randomisation, poor reporting and other risks of bias" (p.21). • "Thirteen of the 16 trials included in this review demonstrated a risk of bias in at least two of several key criteria: random sequence generation; allocation concealment; blinding of participants, outcome assessors and intervention providers; incomplete outcome data; selective outcome reporting; and other sources of bias" (p.25). <u>Strengths</u>: "Overall only three of the 16 included trials were well designed and had a fairly low risk of bias (Fang ZH 2007;	*tang, Tang kang yin*, *Liu wei di huang tang,* and *Xiaoke huayu pian* all showed a significant improvement compared to the control in reducing total cholesterol and triglycerides" (p.24). <u>Mortality, morbidity or cost effectiveness</u>: "No study investigated mortality, morbidity or cost effectiveness" (p.10). <u>Conclusions:</u> "The available evidence suggests that some Chinese herbal medicines could be considered as a potential treatment in people with impaired glucose tolerance and reduce the incidence of diabetes. Given the sources of potential bias further evidence is required to confirm these trends" (p.26).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			Hioki C 2004;Wang BQ 2008)" (p.25).	
Greaves, 2011 SR review of reviews AMSTAR: 55% 30 Total (9 SRs, 17 MA, 3 SR&MA, 1 Review of reviews)	Range of settings: (e.g. home based, leisure centre based, primary care, workplace	Lifestyle: "Interventions promoting **physical activity and/or dietary change** at the individual-level (i.e. interventions delivered to individuals either singly or in group sessions, but not whole community or whole-population level interventions such as media campaigns or changes in the local environment)" (p.2). Follow-up: 1wk- 7yr follow-up range Comparators: Varied	Quality Assessment: • Used the "Overview Quality Assessment Questionnaire (OQAQ) – possible range of 0-18> included review if rated above. This system grades the risk of bias associated with a particular piece of evidence on a hierarchy from meta-analysis and RCT evidence (grade 1) down to expert opinion (grade 4), with additional indicators (++, + or -) to indicate methodological quality. 14" (p.3) • "An evidence grade was given to each reported analysis, based on the Scottish Intercollegiate Guidelines Network (SIGN) evidence grading system" (p.3). • "No statistical analyses or meta-analyses were conducted. Instead, the existing analyses	Weight Loss • "Overall, interventions produced clinically meaningful weight loss (3-5 kg at 12 months; 2-3 kg at 36 months) and increased physical activity (30-60 mins/week of moderate activity at 12-18 months). Based on causal analyses, intervention effectiveness was increased by engaging social support, targeting both diet and physical activity, and using well-defined/established behaviour change techniques. Increased effectiveness was also associated with increased contact frequency and using a specific cluster of "self-regulatory" behaviour change techniques (e.g. goal-setting, self-monitoring). No clear relationships were found between effectiveness and intervention setting, delivery mode, study population or delivery provider. Evidence on long-term effectiveness suggested the need for greater consideration of behaviour maintenance strategies" (p.1). Changes in Physical Activity: • "Interventions produced significant and clinically meaningful changes in physical activity (typically equivalent to 30-60 minutes of walking per week, for up to 18 months) and in weight (typically 3-5 kg at 12 months, 2-3 kg at 36 months). Greater effectiveness of interventions was causally linked (in meta-analyses and randomized trials which

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			reported in the articles reviewed were extracted and reported in a systematic format" (p.3). • "Reviews were included if their OQAQ score was 14 or more (possible range 0-18) and if they scored at least one point for either of the two OQAQ criteria about assessing quality/taking quality into account in analyses (this was intended to maximise the likely quality of evidence underlying the review-level analyses)" (p.3). • "The methodological quality of included reviews (Additional file 1 Tables S4, S6) was generally good (median OQAQ score = 15.6). The most common methodological weaknesses were the lack of use of study quality data to inform analyses (e.g. by	experimentally manipulated the use of these elements) with targeting both diet and physical activity, mobilising social support and the use of well described/established behaviour change techniques. Greater effectiveness was also associated (in correlational analyses and non-randomised comparisons) with using a cluster of self-regulatory techniques (goal-setting, prompting self-monitoring, providing feedback on performance, goal review[62,64]), and providing a higher contact time or frequency of contacts. However, with regard to intensity, the amount of clinical contact in interventions varied widely (see ranges reported above) and the evidence did not support the recommendation of any particular minimum threshold. The evidence on patterns of effectiveness over time[37] also suggested that there is a need for an increased focus on the use of techniques to support behaviour maintenance. There were no clear associations between provider,\ setting, delivery mode, ethnicity and age of the target group and effectiveness. This (and evidence from a range of individual RCTs cited in the reviews examined) suggests that interventions can be delivered successfully by a wide range of providers in a wide range of settings, in group or individual or combined modes, and can be effective for a wide range of ethnic and age groups" (p.8).

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			sensitivity analysis, or by constructing separate analyses which excluded low quality trials) and potential bias in the selection of articles (e.g. not using independent assessors)" (p.5). <u>Strengths:</u> • Focused on higher quality systematic reviews • "Identified a substantial number of reviews which synthesized data from a large number of RCTs and other studies, in a wide range of age groups, clinical/risk groups and settings" (p.9). <u>Limitations:</u> • "Inadequate description of behavioral interventions in the individual study reports"(p.9). • "major limitation in assessing the utility of	<u>Dietary</u> • "Medium and lower quality causal evidence from metaanalyses and descriptive summaries of RCTs (nine analyses from three separate reviews: six medium, three low) that found positive changes in self-reported diet (calorie, fat, fibre, fruit and vegetable intake) at 6 to 19 months of follow up for dietary interventions[38,34,44]" (p.5). <u>Conclusions:</u> • "Interventions to promote changes in diet and/or physical activity in adults with increased risk of diabetes or cardiovascular disease are more likely to be effective if they a) target both diet and physical activity, b) involve the planned use of established behaviour change techniques, c) mobilise social support, and d) have a clear plan for supporting maintenance of behaviour change. They may also benefit from providing a higher frequency or total number of contacts" (p.10). *see paper for more detailed results section for specific quality of evidence for: • Weight loss • Physical activity • Dietary Intake • Behavioral Change • Mode of delivery • Intervention provider • Intervention intensity • Weight loss

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			specific theories and techniques underpinning intervention is that techniques may not be implemented rigorously or may not faithfully represent the specified theories[62,70]"(p.9). • "none of the 30 reviews that we examined took intervention fidelity into account. Hence, the lack of an association between the use of a stated theory and effectiveness may reflect a lack of good theories or it may reflect poor implementation of theories" (p.9). • Sources of bias: measurement issues (especially in relation to the use of self-report data); self-selection of intervention participants; and a failure to consider potential biases due to study quality in some reviews; associative	• Dietary Change • Physical Activity

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			evidence, other covariates than those analysed may account for the stated relationships (e.g. the association between intensity and effectiveness might be explained to some extent by lower quality of intervention being associated with lower intensity; low sample size contributing to some of the analyses examined • "In interpreting the above information, it should be noted that the analyses considered were in many cases based on overlapping sets of trials (and other studies)" (p.9). • "this is a review of reviews we were not able to synthesise or meta-analyse data from individual studies, which may have yielded valuable evidence" (p.10)	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
Hopper, 2011 MA AMSTAR: 45% 10 RCTs	Various locations in the community (worksites, inner city, rural church, medically underserved community, hospital	Lifestyle intervention: **pharmacological intervention** or **non-pharmalogical** (**diet, exercise or diet with exercise)** • Diet and exercise differed between trials • The lifestyle and drug arms were analyzed separately but compared to the same control group. • Pharmacological agents included metformin, acarbose, voglibose, rosiglitazone, pioglitazone, nateglinide, ramipril and valsartan Follow-up: • "Duration of follow-up ranged from 2.8 to 6 years for the intervention arms, with mean intervention time of 3.75 years. Most trials had follow-up only for the time of the intervention, but three studies reported extended follow-ups of 10.6, 20 and 6.5 years (Finnish DPS, DaQing and NAVIGATOR respectively)" (p.815) • "…three studies reported extended follow-ups of 10.6, 20 and 6.5 years (Finnish DPS, DaQing and NAVIGATOR respectively) (p.815) Comparator: A range: placebo, limited health advice, usual care	Quality Assessment: • "Studies evaluated were individually underpowered to examine mortality and cardiovascular outcomes, with generally low cardiovascular risk in patients with pre-diabetes combined with a relatively short follow-up time. When examined together in this meta-analysis, the confidence intervals around the point estimates are wide" (p.821). • "The reasons for the absence of a significant beneficial effect on macrovascular outcomes, despite success in diabetes prevention, could be explained by the interventions and follow-up periods applied in these studies being of too brief duration to influence all-cause and cardiovascular mortality,	Diabetes Prevention: • "Diabetes was delayed or prevented overall (RR 0.66, 0.55–0.80) by intervention versus control (Figure 2), with a heterogeneity x^2 of 267.3 ($p<0.001$). Both non-drug and drug-based approaches reduced progression to overt diabetes. Non-drug approaches (n=3495, 0.52 95%CI 0.46–0.58) were superior ($p<0.05$) to drug-based approaches (n=20,872, 0.70, 0.58–0.85). Diabetes was not prevented in three trials, which included the pioglitazone arm of IDPP-2, the Ramipril arm of DREAM and the nateglinide arm of NAVIGATOR (Figure 2)"(p.817). Weight Loss "The lifestyle interventions in the non-drug trials achieved greater weight loss than those in the drug trials" (p.813). All- Cause Mortality Outcomes • "There was no difference in all-cause mortality with an intervention in prediabetes versus control group (0.96, 0.84–1.10, Figure 3). There was no significant heterogeneity between the trials (heterogeneity x^2 of 6.86, p=0.651). This result was dominated by the NAVIGATOR trial with 62.1% of the weight. There was no difference (p=NS) between non-drug (0.81, 0.61–1.09) and drug approaches (0.99, 0.85–1.15). Sub-group analysis that looked only at trials that prevented

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			or indeed numbers are insufficient to show an effect despite meta-analysis. It may be that non-glycaemic cardiovascular risk factors, including hypertension, dyslipidaemia, hypercoagulability and obesity, have greater impact than glycaemic control on these outcomes. Additionally, the protective effect of preventing diabetes may be masked by'off-target' cardiovascular effects of the therapies themselves" (p.821). <u>Limitations:</u> "Our meta-analysis has several limitations. Some trials included subjects with cardiovascular risk factors, others with previous cardiovascular events, so there is marked variation in risk between the trials. Also, prediabetes was not	diabetes did not alter this result (0.93, 0.80– 1.07), and removal of rosiglitazone did not alter the result (0.96, 0.84–1.09)"(p.817). <u>Cardiovascular outcomes</u> • "Two trials of non-drug approaches 18,19,22,23 and all the pharmacological interventions recorded cardiovascular death. There was no overall difference in risk of cardiovascular death in the intervention vs the control group (1.04, 0.61–1.78 p=NS, Figure 5) with a heterogeneity x^2 of 13.30 (p=0.038). There was a non-significant trend towards increased cardiovascular death when the drug sub-group alone was considered (1.27, 0.96–1.68, p=NS), and a non-significant trend towards reduction in cardiovascular death when the non-drug sub-group (0.70, 0.46–1.07 p=NS) was assessed. This result did not change when only trials that prevented diabetes were examined (1.06, 0.83–1.36) or with the removal of rosiglitazone (1.10, 0.87–1.40)" (p.821). <u>Myocardial Infarction and Stroke outcomes</u> • "Only four drug trials contributed data to this endpoint. There was a 41% relative risk reduction in fatal and non-fatal myocardial infarctions; however, this result failed to reach statistical significance (RR 0.59, 0.23– 1.50 p=NS, Figure 6) with a heterogeneity x^2 of 9.64, p=0.022" (p.821). <u>Conclusions:</u>

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			addressed in isolation, with other risk factors optimised according to guidelines. When identified, elevated blood pressure and dyslipidaemia were referred back to the local doctor for treatment. These results were secondary outcomes pooled from trials looking at development of diabetes in prediabetic subjects, not necessarily cardiovascular outcomes. Although the larger trials predefined cardiovascular endpoints that were adjudicated, other studies relied on reporting from national agencies or hospital records. Thus, the reliability of these reports compared with adjudicated reports is questionable. Additionally, we did not have access to the original source data. A further limitation of this specific study is the revising downwards of the definition of IGT and IFG over time, meaning that in earlier	• "The present meta-analysis found overall that with interventions targeting prediabetes for an average 3.75 years, there was no reduction in all-cause or cardiovascular mortality. A non-significant trend towards reduced risk of fatal and non-fatal myocardial infarction was observed, and fatal and non-fatal stroke was borderline reduced. A clear reduction in progression to type 2 diabetes occurred with these interventions, with intensive lifestyle therapy being superior to drug treatments, although with smaller numbers of subjects evaluated" (p.821). • "Based on this analysis in prediabetes, together with trials in patients with overt type 2 diabetes mellitus, the role of glucose lowering in the prevention of cardiovascular events remains unclear" (p.821). • "**In conclusion, despite interventions in pre-diabetes being mostly successful in retarding the progression to overt diabetes, this did not result in reduced all-cause mortality or cardiovascular mortality**" (p.822).

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			studies, some participants would have been enrolled in the study with what would later be considered diabetes; however given the size of the changes in the definition, we expect this effect to be minimal" (p.821).	
Johnson, Jones, 2013 SR (qualitative AMSTAR: 55% 19(from 17 studies)	14 USA 1 Germany 3 Finland 1 Australia	**Lifestyle: Dietary and Physical Activity Interventions** • "'Translational research' has been described as the assessment of smaller programmes in 'real-world' settings, where resources are more limited and samples less selective than in the trial environment" (p.3) • "lifestyle interventions based on protocols that were replicable and that had been shown to have some success in preventing or delaying Type 2 diabetes"(p.4) • "The programmes included a dietary as well as a physical activity component to the intervention, as with the DPP and DPS protocols. As in the original trials, trained personnel such as nurses, dieticians and physical fitness experts were recruited to deliver the interventions in all but one study, where community members were trained to	<u>Qualitative Assessment:</u> • "27-item tool for the assessment of quantitative studies recommended in the NICE methods manual"(p.4) • "Generally, the quality of the included studies was moderate to good (see also Supporting Information, Appendix S2). No included study complied with all of the 27 quality criteria in the assessment tool [12], although this was mainly attributable to the range of study types included and the complexity of the intervention" (p.4). • "Reporting of weight loss outcomes differed	<u>Weight change:</u> • "The main outcome that was reported in all studies was weight change. Weight loss, which occurred in all but one study, was greater in intervention arms than in control subjects. No consistent differences were found in blood glucose or waist circumference" (p.3). • "Included randomized controlled trials [14(Kulzer, 2009),15(Katula, 2011),22(Ackermann, 2008)] reported greater weight loss (at least 4.0%) in the intervention arm than in the control groups (no greater than 2.0%)" (p.8). • "Non-randomized studies also reported weight loss" (p.8) • "Only one non-randomized study reported no weight loss [16(Faridi, 2009)], with a mean gain in weight of 0.2% in the intervention arm and 0.4% in control subjects. However, there were reported significant differences in baseline characteristics of intervention and control groups" (p.11). • "Whilst the findings varied widely in terms of effect size, there was a strong trend toward

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		carry out a church-based intervention."(p.8) Follow-up: ranged from 16 weeks to 3 years, with 12 studies providing results from a follow-up of at least 12 months Comparator: A range: usual care, minimal health instruction	between studies and included mean weight reduction, percentage weight reduction or the percentage achieving a specified weight loss. Much of the detail regarding delivery of interventions was not reported. This degree of heterogeneity was deemed not appropriate for a meta-analysis"(p.12). Limitations: "This review has assessed only those studies that applied a specified, known protocol that has previously been associated with a reduction in the incidence of Type 2 diabetes as well as weight loss. Given the relatively short follow-up and smaller sample size, translational studies were more likely to	weight loss following all but one of the interventions" (p.12). • "Studies that included a comparator reported greater effects in the intervention arm than in the control subjects"(p.12) • "This review demonstrates that group based interventions can yield significant weight loss (with the expectation of reductions in the risk of Type 2 diabetes), provided that changes are sustained over a number of years" (p.13). Changes in Waist circumference: • "Changes in waist circumference were reported in seven studies. In two randomized controlled trials, reductions of at least 4 cm were reported in the intervention arm compared with less than 0.6 cm in the controls after 12 months [14(Kulzer, 2009),15(Katula, 2011)]. Single-group studies based on both the DPP and DPS also reported reductions of between 1.6 and 4.3 cm at 12 months [14(Kulzer, 2009),19(Absetz,2009),21(Laatikainen, 2007),31(Seidel, 2008)], although in one study this was not sustained at 3 years [20(Saaristo, 2010)]" (p.11). Diabetes Incidence: • "Translational studies based on the intensive diabetes prevention programmes showed that there is potential for less intensive interventions both to be feasible and to have an impact on

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			have sufficient statistical power to measure change in weight than in diabetes incidence. However, weight loss is associated with a reduction in diabetes incidence"(p.13).	future progression to diabetes in at-risk individuals" (p.3). • "Reduction in diabetes incidence was not measured in any controlled study. This may reflect the difficulty assessing incidence within the short duration of the included studies" (p.13). <u>Conclusions:</u> • "Findings from this review suggest that significant weight loss may be achievable with larger groups than are currently adopted in clinical practice, with some DPP translation studies using classes of 15 [24(Almeida, 2011)] and 17 participants [17(Amundson, 2009)]. Equally important is the skill of the educators [34]. There was a variety of professional backgrounds amongst the educators in the studies in this review, with associated variation in costs. Further research is needed to identify the most cost-effective mode of delivery. From the findings of the included papers, one option may be a highly qualified diet and physical activity professional supported by a less-qualified individual" (p.13). • "Our review supports the findings that significant effects from translational lifestyle interventions on clinical parameters such as blood glucose and diabetes risk may be difficult to demonstrate, and that decreases in weight following adapted interventions are a more promising finding [36]" (p.13).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				• "Translational studies based on the DPP and the DPS, but with modifications to increase feasibility, reported mean and percentage weight loss (as well as reductions in waist circumference) in a range of settings. Weight loss is associated with diabetes prevention and so can be regarded as a marker for potential prevention over the longer term, although current evidence for sustainability beyond 3 years is limited. There is therefore potential, given that the lower costs of group-based interventions lessens financial barriers to implementation, for interventions to have an impact on future progression to diabetes in at-risk individuals in 'realworld' settings. More long-term research is required to assess the sustainability and long-term outcomes of translational interventions" (p.13).
Malkawi, 2012 SR AMSTAR: 27% 14/19 RCTs	USA 5 UK 4 Finland 5 China 1 Brazil 1 India 1 Netherlands 1 Australia 1	**Lifestyle: Physical activity and or diet** • "This review included interventions which promote physical activity either separately or as part of a lifestyle or dietary intervention" (p.2) • "Only well-structured interventions which promoted exercise or physical activity were included" (p.2) Two of the following (p.3) - Curriculum based interventions (interventions delivered according to certain syllabus). - Interventions which contained individual (face to face) sessions.	Quality Assessment: • "The quality and strength of each paper included in this review can lead to different results" (p.5). Limitations: • "This systematic review has many limitations. It only included English language articles. Many high quality articles which are written in	Overall: • "The review found strong evidence regarding the effectiveness of well-structured physical activity interventions in reducing the incidence of type 2 diabetes. Moreover, well-structured interventions were also found to be effective in restoring glucose measures including fasting plasma glucose and 2h plasma glucose. However, there was weak evidence regarding the effectiveness of well-structured interventions in increasing the level of physical activity. The review suggests using well-structured lifestyle interventions which include both physical activity and dietary advice. More research regarding the effectiveness of single

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		- Interventions which used additional supportive materials or equipment including advice leaflets and pedometer. - Theory based interventions or interventions which used a counseling approach for changing behaviors (this should be clearly stated by the author). - Interventions which included teaching behavior change strategies such as goal setting, action planning and self-monitoring. - Interventions which included clearly defined exercise recommendations including exercise type, frequency and duration (such as 30 minutes brisk walk per day) or detailed specific supervised exercise sessions. - Interventions which were developed or delivered by experts or trained facilitator. <u>Mode of Delivery:</u> • Individual face to face sessions • Counseling approach • Supervised exercise sessions <u>Follow up range</u>: 3mons-10yr <u>Comparator:</u> Placebo or mini intervention (general lifestyle advice)	German, French and Swedish may not included and this may affect the final results. This review included only published articles, excluding grey literature (unpublished literature) can make the review prone to publication bias." • "Moreover, including only published literature may ignore hidden evidences which could be relevant to this review. Factors related to time restraints in addition to that it is based on a single novice researcher effort the thing which makes it not as thorough as an experienced research team [56]. Most of the interventions which were included in this review excluded participants with certain medical conditions such as cardiovascular	physical activity interventions in preventing type 2 diabetes is recommended" (p.1). <u>Effect of well-structured interventions on reducing glucose measures</u> • "In summary, there is good evidence that effectiveness of well-structured interventions can improve glucose measures. Most of the positive results came from the US and Finnish diabetes prevention programs which have larger sample size and long follow up period (see the results table)" (p.4). <u>The effect of well-structured interventions on reducing the incidence of T2D</u> • "All studies which were identified found a significant reduction in the cumulative incidence of diabetes including Tuomilehto et al., (2001), Ramachandran et al., (2006), Knowler et al., 2002, Pan et al., 1997, Diabetes Prevention Program Research Group et al., 2000 and Lindström et al., (2003 b) [22,23,30,36,41,43]" (p.4). • "The studies which measured the incidence of type 2 diabetes gave better indication regarding the effectiveness of these programs because studies may find significant improvement in fasting plasma glucose or 2 hour plasma glucose measures among participants, but it was difficult to determine if there was an actual reduction in the number of patients with diabetes" (p.4).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		"the nature of the control group, it differed from one study to another. Most of the trials provided the control group with a mini intervention for ethical reasons"(p.5)	diseases for ethical reasons. This may lead to exclusion of a large population who are at risk of developing type 2 diabetes"(p.4).	<u>The effect of well-structured interventions on increasing the level of physical activity</u> • (5 studies found no sig improvement after 6-18 mon follow up[Thompson et al., 2008; Greaves et al, 2008; Kinmonth et al,2008; Sartorelli et al., 2005; Allen et al.,2008] & 5 found sig improvement after 1yr follow up [Laatikainen et al., 2007; Lindstrom et al., 2003a; Tuomilehto et al., 2001; Yates et al., 2009; Lindstrom et al., 2003b] • "there is weak evidence regarding the effectiveness of well-structured interventions in increasing the level of physical activity as the majority of studies relied only on self-reported data in addition to the fact that it is difficult to measure physical activity in general" (p.5). <u>Can PA alone be enough to prevent diabetes?</u> • (based on 4 studies that studied PA alone [Kinmonth et al, 2008; Yates et al., 2009; Yang et al., 2009; Yates et al., 2009]) most of the positive results were recorded from lifestyle interventions which included both diet and lifestyle counseling. Therefore, it is difficult to confirm that physical activity alone is enough to prevent type 2 diabetes and there is still a need for more research in this area. • "The results found a potential effectiveness of well-structured interventions which include promoting physical activity especially in terms of

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				reducing diabetes incidence and improving glucose measures" (p.5). <u>Common elements:</u> • "Most of the studies which found positive results regarding the effect of well-structured interventions were conducted according to the Finnish, US, Chinese and Indian diabetes prevention programs in addition to PREPARE intervention (the UK program). The most common themes between all these interventions are that they were conducted at national level, had clearly defined physical activity objectives (such as 30 minutes of daily walking) and were more likely to provide personal counseling sessions. In addition, most of them were lifestyle programs (included both dietary and exercise interventions). Lifestyle interventions were considered too expensive as a result of the cost of delivering the intervention including trained health care educators, the cost of exercise equipment and the cost of participant's time [45]. On the other hand, lifestyle interventions have multiple positive health outcomes including reducing the body mass index, improving blood pressure, prevention of hypertension and many chronic illnesses [46]" (p.5). <u>Conclusions</u>: • "This review found that there is a good evidence of the effectiveness of well-structured

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				interventions in reducing glucose measures and stronger evidence regarding reduction in the incidence of type 2 diabetes. However, it found weak evidence regarding the effectiveness of well-structured interventions in increasing the level of physical activity because most of the studies rely on self-reported questionnaires" (p.7). • "this review cannot give any recommendations regarding the type, duration and intensity of physical activity which is more effective in prevention of diabetes" (p.7) • "There is need for more research to confirm if physical activity alone can be enough to prevent type 2 diabetes. Moreover, it is recommended to implement lifestyle interventions because most of the positive results were recorded from them and they have many other health benefits. Before implementing a physical activity intervention anywhere, it is important to ensure that it has clearly defined objectives and process of evaluation in addition to implementing culturally accepted interventions. It is important to apply more effective ways to identify people who are at high risk of type 2 diabetes rather than relying on GPs. In addition, it is recommended to support these interventions with adequate infrastructure" (p.7).
Merlotti, 2014 SR, MA AMSTAR: 64%	Any setting	"studies were grouped into 15 different strategies, independently of the original aim of the studies (*ad-hoc* interventions or *post-hoc* analysis), and of the nature of	<u>Quality Assessment:</u> • "In some studies there were more arms with different strategies; in	<u>Prevention of new diabetes cases</u> • "In all studies considered together (RCT, NRCT and OBS), effectiveness in prevention of new cases of diabetes was shown, as OR was 0.621 (C.I. 0.579–

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
71(56 studies were randomized, while 16 studies were not randomized)		studies (randomized or not-randomized trials, observational studies): • diet plus physical activity, • physical activity, • anti-diabetic drugs (glitazones, beta-cell stimulating drugs, metformin), • cardiovascular drugs (ACE inhibitors and ARB, • calcium-blocking agents, • other strategies (diets, lipid-affecting drugs, vitamins and micronutrients, estrogens, alcohol, coffee) • and bariatric surgery"p720 <u>Follow up:</u> "Duration of follow-up was different between groups, being less than 5 years in groups 1, 3, 4, 6, 7 and 8" (p.721). <u>Comparator</u>: "the difference in the incidence of new cases of diabetes in the intervention group and in the control group" (p.720)	such cases, the same study was considered more than once in the analysis, in the figures, and in Table 1 and Table S1. In some studies, not all items under evaluation were appropriately reported with measure of dispersion; therefore, meta-analysis was possible only for selected items. Quality of reports was assessed according to Jadad et al. [95], that is, description of random allocation, blinding, clear and validated outcomes, description of dropouts and withdrawals. Appropriate methodology according to the PRISMA statement [96] was adhered to, as shown in flow diagram (Figure 1)" (p.720). • "Heterogeneity was assessed through Q (the Cochran's heterogeneity statistics) and I2 [98]	0.668); OR was 0.561 in NRCT (C.I. 0.471–0.668), 0.652 in RCT (C.I. 0.605–0.702) and 0.688 in OBS (C.I. 0.603–0.786)" (p.721). • "All strategies considered in meta-analysis reduced the risk of T2DM, with the exception of beta-cell stimulating drugs, vitamins and estrogens (Figure 2), with the following order of effectiveness; bariatric surgery (OR 0.16), followed by glitazones (OR 0.37), diet+physical activity (OR 0.43), diets (OR 0.44), physical activity or education (OR 0.53), alfa-glucosidase inhibitors (OR 0.54), metformin (OR 0.65), lipid-affecting drugs (OR 0.66), alcohol (OR 0.65) and cardiovascular drugs (OR 0.74–0.76)" (p.721) • **Drugs:** **"**ARB were more effective than beta-blockers and Ca-channel-blockers [72(Dahlof, 2002),77(Kjeldsen, 2006)], Ca-channel-blockers were more effective than beta-blockers and diuretics [80(Mancia, 2003),82(Cooper-DeHoff)] and ramipril, not Ca-channel-blockers, was more effective than diuretics [75(Barzilay 2006),78(Black, 2008)]. Therefore, group 7 [i.e. ACE-inhibitors + ARB or ACE-inhibitors alone, or ARB alone vs control] was also further analysed by taking into account only studies comparing ACE inhibitors or ARB versus placebo; in such studies, the OR was 0.82 (0.75–0.91, not shown)" (p.721) "Our data support and expand previous meta-analyses considering ACE inhibitors and ARBs [92–94], showing that also calcium antagonists were

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			statistics (the percentage of variation not due to chance) for each comparison, and potential sources of heterogeneity were discussed where appropriate. A p value<0.05 was considered indicative of statistically significant heterogeneity" (p.720). • "Jadad's score was significantly lower in groups 13 and 14 than in the remaining groups (not shown)."p721 • "Heterogeneity was significant when all studies were considered together; in contrast, heterogeneity was not significant in groups 1 (diet+physical activity), 4 (metformin), 6 (Alfa-glucosidase-inhibitors), 9 (diets), 10 (lipid-affectingdrugs), 13 (alcohol) and 14 (coffee), of borderline statistical significance in group 15	effective in preventing T2DM. With one exception [55(Gerstein, 2011)], studies with ACE inhibitors, ARBs and calcium antagonists were used to compare the validity of complex treatment regimens on arterial hypertension, on ischemic heart disease, on prevention of cardiovascular events, that is, for purposes other than prevention of T2DM. Therefore, only a few comparisons were with placebo, and showed better effect than placebo (ACE inhibitors or ARB, 55 [Gerstein, 2011], 71[Yusuf, 2001], 73[Yusuf, 2005], 74[Yusuf, 2005], 76[Bosch, 2006], 79[McMurray, 2010]); indeed, the OR of ACE inhibitors and ARB versus placebo was only 0.82, while the OR of group 7 and 8 were 0.74–0.76. Meta-regression indicates that significant predictors of effectiveness are represented by age of subjects and by amount of weight lost" (p.723). • **Bariatric surgery:** "subjects undergoing bariatric surgery are completely different from other subjects. This raises two concepts, that are not mutually exclusive: one is that for morbidly obese subjects weight loss is an adequate measure to prevent T2DM; the other is that T2DM is a different disease in overweight and in morbidly obese subjects; intuitively, the fact that T2DM appears in subjects with an excessive BMI, and often disappears after weight loss [102,103], suggests that the derangement of beta cells is of a lower degree, or that the mechanisms involved are different" (p.722)

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			(bariatric surgery, p<0.05), significant in groups 2 (physical activity or education), 3 (glitazones),7 (ACE-inhibitors+ARB), 8 (Ca-channel-blockers) (always p<0.01); heterogeneity disappeared in group 7 when ARB were considered alone. Heterogeneity was not reduced by taking into account size of study, year of publication, duration of follow-up, and other conditions at baseline (when reported); when stratified by criteria of diagnosis, heterogeneity dropped in groups 3, 8, and 15 from 79.1% to 38.3%, from 71.1% to 17.3%, and from 62.1% to 10.4%, but remained statistically significant" (p.721). • "In the secondary analysis, aimed at	<u>Conclusions:</u> • "These data indicate that several strategies prevent T2DM, making it possible to make a choice for the individual subject" (p.719) • "Most preventive strategies presented in this meta-analysis (intensive lifestyle modification, anti-diabetic and cardiovascular medications, bariatric surgery) are effective in the prevention of T2DM, the most effective strategy being bariatric surgery. It should however be noted that the group undergoing bariatric surgery was different from the other groups for BMI. Therefore, for obese patients, the strategy to prevent T2DM may be bariatric surgery, while overweight and lean subjects might benefit from other approaches, like intensive lifestyle modification and/or drugs. In addition, age of subjects and loss of weight are important in determining effectiveness of intervention. Opportunistic strategies might also be employed; dealing with a hypertensive patient, ACE inhibitors ARBs should represent the first choice, followed by calcium antagonists, while diuretics should be avoided or limited; dealing with hyperlipidemic patients, one should consider that prevention of diabetes is possible with fibrates, not with statins [104], even though prevention of major cardiovascular events is probably more effective with statins than with fibrates [108]."p724

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			evaluation of the existence of a potential publication bias (Figure 3), from inspection of the funnel plots [99] we concluded that symmetry existed for NRCT, not for RCT, indicating publication bias. At the Egger's test [100], publication bias was present only for group 15 (bariatric surgery, p=0.033)" (p.722). <u>Limitations: (p. 724)</u> **Heterogeneity** • "found in a few classes of drugs or strategies making comparisons difficult to be fully reliable, and to be taken with caution" • "….strategies were not fully comparable in terms of completeness of details; e.g. severity of baseline conditions (IGT or IFG) was not considered in some	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			groups (Table 1),making conclusions hard to stand" • "…..quality of studies (Jadad's score, 95) was lower in two groups as compared to the remaining studies." • "Heterogeneity was not decreased by taking into account BMI, age, size of study, year of publication, duration of follow-up, conditions at baseline (when reported), duration of follow-up, fasting and 2 h glucose, fasting and 2 h insulin levels, ethnicity and weight loss; analysis of criteria employed for diagnosis of T2DM (interview, fasting blood glucose, oral glucose tolerance test) reduced but did not abolish heterogeneity." **Possible selection bias** • "Some studies were randomized, while several studies were not	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			randomized, and a few studies were observational, even though all studies were controlled" (p.724). **Publication bias (p.724)** • "….negative results might not been published; for instance, statins may have a negative effect on incident T2DM [104], at difference from fibrates and orlistat." • "….present when considering all studies together, and in RCTs, but not in NRCTs, and we can interpret this finding as due to heterogeneity of findings of different strategies." • "Among individual strategies, publication bias was only present in bariatric surgery, and this asks for caution in interpretation of results; however, we cannot dismiss these findings, that are supported by a	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			meta-analysis [102] and by three randomized trials showing resolution of T2DM after bariatric surgery [103]." Studies with **anti-diabetic drugs** consider: (p.724) • "….whether prevention, masking of pre-existing diabetes or post-ponement of diagnosis [105].Criteria for diagnosis were heterogeneous, and using simple fasting blood glucose can lead to different figures from use of oral glucose tolerance test." • "…. consider that different approaches can have a different impact depending on pre-existing conditions; for instance, in the DPP study, it was shown that metformin and exercise have a different effect depending on age of subjects under study [27]. Data from meta-	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			regression support the importance of age of subjects, aswell of the amount of weight lost." • "….prevention cannot be indefinite; for instance, after disappearance due to bariatric surgery, diabetes can re-appear [106], and catch-up of diabetes has been reported after stopping preventive medical treatments [60,107]." **duration of follow-up** • "…was greatly different in different groups, so that probably effectiveness was not fully explored, at least in studies with a short follow-up" (p.724) **population** • "…the majority of subjects studied was caucasian, so that we have little information on other ethnic groups" (p.724)	
Phung, Baker,	Not reported	Drug: Use of oral antidiabetic **drug** classes:	Quality assessment:	Return to normoglycemia:

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
Tongbram 2012 MA AMSTAR: 64% 13 RCTs studies		• thiazolidinediones, biguanides, a-glucosidase inhibitors, sulfonylureas, meglitinides, or dipeptidyl peptidase-4 inhibitors; • "About 80% of the studies reported concurrent lifestyle modification in the form of advice on healthy diet and physical activity along with the intervention" Follow up: ranged from 0.25-5 years (median 1 year) Comparator: Placebo or non-active control	• Jadad scale:"Jadad scale assesses inherent controllers of bias by assessing randomization, double-blinding, and patient withdrawals. An aggregate score between 0 and 5 was calculated for each included trial (0 = weakest, 5 = strongest). Trials scoring less than 3 were deemed to have lower methodologic quality."p470 • "For the overall meta-analysis of oral antidiabetic drugs versus placebo/control, there was a high level of statistical heterogeneity between included trials (I^2 = 80%). In the comparison of individual drug classes and placebo/control, low, moderate, and high levels of statistical heterogeneity were found for thiazolidinediones (I^2 =	• "Upon meta-analysis, the use of oral antidiabetic drugs resulted in approximately doubling the odds of restoring normoglycemia compared to placebo/control (OR 2.03, 95% CI 1.54 to 2.67). When individual classes of oral antidiabetic drugs were evaluated separately, thiazolidinediones (OR 2.33, 95% CI 1.93 to 2.81) and a-glucosidase inhibitors (OR 2.02, 95% CI 1.26 to 3.24) were associated with significantly increased odds of patients regressing to normoglycemia. Biguanides (OR 2.04, 95% CI 0.38 to 9.09) and sulfonylureas (OR 1.84, 95% CI 0.38 to 9.09) failed to reach our a priori threshold for statistical significance (Figure 2). Upon sensitivity analyses, excluding trials that did not incorporate any dietary advice or modification (OR 1.91, 95% CI 1.42 to2.57), excluding trials with a Jadad score less than 3 (OR 1.66, 95% CI 1.21 to 2.29), and excluding trials evaluating troglitazone (OR 1.97, 95% CI 1.47 to 2.65), the use of oral antidiabetic drugs still showed statistically significant improvements compared to placebo/control. When excluding trials evaluating troglitazone, thiazolidinediones as a class still showed statistically significant improvements compared to placebo/control (OR 2.28, 95% CI 1.84 to 2.83)" (p.471). • "Our meta-analysis of 13 trials (N = 11,600) showed that use of oral antidiabetic drugs was associated with a statistically significant 2-fold increase in the odds of patients with prediabetes regressing to normoglycemia compared to

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			12.6%), biguanides (I^2 = 67.9%), and a-glucosidase inhibitors (I^2 = 81.7%), respectively. Statistical heterogeneity could not be assessed for sulfonylureas, as only one trial was identified. There was low likelihood of publication bias in our meta-analysis (p = 0.55)" (p.473). <u>Limitations:</u> • "Although troglitazone is not available for use because of safety concerns, trials evaluating troglitazone were included in the meta-analysis to add valuable insight into drug efficacy and to increase statistical power in the analysis of thiazolidinediones as a class. When excluding trials evaluating troglitazone, results remained statistically significant for the	placebo/control; thiazolidinediones and a-glucosidase inhibitors individually provided 2-fold significant increases in the odds of regressing to normoglycemia. Biguanides and sulfonylureas failed to show statistically significant effects on regression to normoglycemia, but positive trends were observed for each of these drug classes. It may be worthwhile to make normoglycemia, rather than simply the maintenance of prediabetes, the therapeutic goal of prediabetes treatment because of the risks of cardiovascular mortality and all-cause mortality associated with prediabetes" (p.473). <u>Conclusions:</u> • "In patients with prediabetes, the use of oral antidiabetic drugs was associated with increased odds of regression to normoglycemia compared to placebo/control. When each drug class was evaluated individually, thiazolidinediones and a-glucosidase inhibitors provided a significant increase in the odds of regression to normoglycemia. However, biguanides and sulfonylureas failed to show statistically significant effects on regression to normoglycemia" (p.475).

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			analyses of both oral antidiabetic drugs in general and thiazolidinediones specifically" (p.474). • "were unable to show statistically significant benefits of biguanides and sulfonylureas on regression to normoglycemia; these negative findings may be a result of underpowered analyses. Since the inclusion criteria and screening of articles were driven by reporting of outcomes, only a single study evaluating sulfonylureas was identified, and conclusions for this class of drug are limited"(p.474) • "doses of oral antidiabetic drugs were not titrated to achieve normoglycemia or specific glucose goals. The timing of normoglycemia	

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			measurement was not reported and it is uncertain whether this is a sustained effect. Varying definitions for normoglycemia criteria (based either on ADA or WHO criteria) may have influenced therate of response"(p.474) • "concurrent use of lifestyle modification could have contributed to the regression to normoglycemia, thereby blunting the effect of the oral antidiabetic drug therapy" (p.475) • "Sensitivity analysis that looked solely at trials including dietary advice or modification did not alter conclusions about the efficacy of oral antidiabetic drugs in regression to normoglycemia" (p.475). • "…although significant heterogeneity was detected, effects seen in trials were of a similar	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			direction of effect, with differences seen in magnitude. Since larger, more precise trials in this meta-analysis showed effects closer to the line of unity, observed statistical heterogeneity likely resulted in an underestimation of treatment effect" (p.475)	
Phung, Sood, 2011 MA AMSTAR: 64% 20 RCT trials	Not reported	Drug therapy: Oral **Anti-diabetic drugs** Follow up ranged from 0.3 - 7yrs (median 2.7 years) Comparator: (placebo-treated, untreated control or active control)	Quality assessment: • Jadad scale • "In traditional meta-analysis, moderate-to high degrees of statistical heterogeneity were detected in the analyses of all treatments vs. placebo / control and alphaglucosidase inhibitors vs. placebo / control, although all studies showed similar direction of effect. A low likelihood for publication bias was expected (P > 0.18 for all)" (p.950). Limitations:	Incidence of new onset diabetes: • "Upon mixed-treatment comparison meta-analysis, thiazolidinediones, alpha-glucosidase inhibitors and biguanides significantly reduced the relative risk of developing diabetes by 64, 40 and 27%, respectively, compared with control. Sulphonylureas and glinides showed no significant effect. Moreover, thiazolidinediones significantly reduced the relative risk of diabetes by 50% compared with biguanides and trended towards a 40% risk reduction vs. alpha-glucosidase inhibitors [relative risk 0.60 (95% credible intervals 0.34–1.02)]. None of the results were appreciably altered upon subgroup or sensitivity analyses. When evaluating risk differences compared with control, thiazolidinediones -9%, number needed to treat = 11), alpha-glucosidase inhibitors -7%, number needed to treat = 14) and biguanides -7%, number needed to treat = 14) continued to show significant benefit" (p.948).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• "First, although troglitazone and phenformin are not available in the USA as a result of safety concerns, they were included in this meta-analysis because we felt they added valuable insight into the efficacy of their respective drug classes and increased statistical power when comparing oral anti-diabetic drug classes. However, we did provide results of a sensitivity analysis excluding these drugs and the comparative efficacy of the oral anti-diabetic drug classes remained consistent with our base-case results. Secondly, our systematic review only indentified eligible trials utilizing first-generation sulphonylureas " (p.962). • "Therefore, there is insufficient evidence to	• "Of the oral anti-diabetic drugs evaluated to prevent Type 2 diabetes, thiazolidinediones were associated with the greatest risk reduction compared with control and associated with greater risk reduction than biguanides. Alpha-glucosidase inhibitors and biguanides performed similarly, and better than control, while sulphonylureas and glinides provided no significant benefit" (p.948). • "Upon traditional meta-analysis, the use of any oral antidiabetic drug statistically significantly reduced the relative risk of developing Type 2 diabetes by 39% compared with placebo／non-active control (Table 3, Fig. 2).Biguanides, thiazolidinediones and alpha-glucosidase inhibitors were associated with decreased relative risk and risk difference of developing diabetes compared with placebo／control upon traditional meta-analysis (Figs 2 and 3). Upon mixed-treatment comparison meta-analysis (Tables 3 and 4, Figs 4 and 5), compared with placebo／control, biguanides (relative risk 0.73; risk difference) 0.07), thiazolidinediones (relative risk 0.36; risk difference)0.09) and alpha-glucosidase inhibitors (relative risk 0.60; risk difference)0.07) were associated with significant benefit in the prevention of diabetes. Sulphonylureas and glinides were not associated with alterations in the risk of development of diabetes in either traditional or mixed-treatment comparison meta-analysis. In cases where both traditional and

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			definitively refute the efficacy of sulphonylureas in the prevention of diabetes. Next, some of the trials included in our meta-analysis utilized concurrent lifestyle modification in addition to oral anti-diabetic drugs or placebo. While this theoretically could impact our results, upon sensitivity analysis limited to trials including lifestyle modification or advice, we found similar results to our base case, suggesting that lifestyle modifications alone may not be sufficient and that oral anti-diabetic drugs may provide additional benefits. Finally, our meta-analysis did not evaluate dipeptidyl peptidase-4 inhibitors or combinations of agents because of a paucity of published trial data" (p.963).	mixed-treatment comparison meta-analysis could be performed, there were no qualitative differences between results, suggesting coherence between methodologies" (p.950). • "traditional and mixed-treatment comparison metaanalysis, alpha-glucosidase inhibitors, biguanides and thiazolidinediones individually reduced the relative risk of diabetes by 23% to 63%. No benefit was seen with sulphonylureas or glinides. Our mixed-treatment comparison meta-analysis demonstrated that thiazolidinediones were associated with less risk of diabetes development than biguanides (relative risk 0.49, 95% credible interval 0.28–0.84) and just missed obtaining statistically significant reductions compared with alpha-glucosidase inhibitors (relative risk 0.60, 95%credible interval 0.34–1.02), providing important new data regarding the comparative efficacy of oral anti-diabetic drugs in the prevention of diabetes" (p.951). • "The corresponding numbers needed to treat from our meta-analysis were 11 for thiazolidinediones and 14 for alpha-glucosidase inhibitors and biguanides (vs. placebo／non-active control) over a median of 2.7 years, suggesting that there may be sufficient evidence to consider using other oral anti-diabetic drug classes, as well as treating patients with a less rigorous definition of 'high risk'" (p.958). • "In addition to efficacy in preventing diabetes, other oral antidiabetic drug selection

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			"Funding for this study was provided by Takeda Pharmaceuticals NorthAmerica Inc. OJP and CIC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis " (p.963).	considerations include contraindications, adverse events and ⁄ or other therapeutic benefits. We were unable to quantify the effect of each oral anti-diabetic drug class on adverse events because of inconsistent reporting. Although thiazolidinediones were found to be most effective, they are not without adverse effects. Of the trials which reported it, patients taking thiazolidinediones gained up to 3.1 kg more in body weight than those taking placebo [3,6]" (p.962).
Schellenberg, 2013 AMSTAR: 91% 9 RCTs	Not reported	Lifestyle: (3 months' duration) The lifestyle intervention had to include **exercise, diet, and at least 1 other component** (such as counseling, smoking cessation, and behavior modification) • "The interventions were administered or delivered by dietitians (21–24, 26–28), exercise advisors (22, 23), physiotherapists (27), nurse managers (22, 23), nurses (21, 24), physicians (22–24), endocrinologists (21), psychologists (22), and technicians (24)" (p.545). Follow ups: between 3-20yrs for 5 RCTs, no follow up for 4 Median follow up = 10yrs Comparator:	Quality assessment: • Cochrane Collaboration Risk-of-Bias tool used to assess risk • "Three trials (22[Knowler, 2002], 26[Mensink, 2003], 28[pinkston, 2006]) were assessed as having high risk of bias, and 6 (21[Bo, 2007], 23–25[Eriksson, 1999; Pan, 1997; Oh, 2010], 27[Oldroyd, 2001], 29[Lu, 2011]) had unclear risk of bias. Most had inadequate allocation concealment. All but 1 study (24[Pan, 1997]) had high or unclear risk of bias for	Progression to Diabetes: • "…7 studies reported that lifestyle interventions decreased the risk for diabetes from the end of intervention up to 10 yrs after it" (p.543) • "Comprehensive lifestyle interventions effectively decrease the incidence of type 2 diabetes in high-risk patients" (p.543). • "The strength of evidence was moderate for development of type 2 diabetes."p546 (7 studies 21-24[Bo, 2007; Knowler, 2002; Eriksson, 1999; Pan, 1997],26[Mensink, 2003], 27[Oldroyd, 2001], 29[Lu, 2011]) (p.546) • "Moderate-strength evidence showed that participation in a comprehensive lifestyle intervention reduced the risk for type 2 diabetes in persons who are at increased risk (Diabetes Prevention Program [22(Knowler), 46], Finnish Diabetes Prevention Study [23(Eriksson, 1999)], European Diabetes Prevention Study–Newcastle [27(Oldroyd, 2001)], Study on Lifestyle

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		Usual Care, diet or exercise components alone or wait list "…comparison group received various interventions, including usual care by a family physician (21, 27), educational materials or advice on diet or exercise (22–26), waitlist controls (28), food diaries (23), and annual diabetes education sessions (29)" (p.545).	lack of blinding for subjective or self-reported outcomes (such as hours of exercise per week). Two studies (22[Knowler, 2002], 28[Pinkston, 2006]) received funding from industry" (p.545). <u>Strengths:</u> "The strength of evidence was assessed using the Agency for Healthcare Research and Quality Evidence based Practice Centre Approach. "Four domains were examined: risk of bias, consistency, directness, and precision. We assigned an overall strength of evidence grade of high, moderate, low, or insufficient. When only 1 study was available for an outcome, we rated the strength of evidence as insufficient" (p.544). <u>Limitations:</u>	Intervention and Impaired Glucose Tolerance Maastricht [26(Mensink)], Da Qing Diabetes Prevention Trial [24(Pan, 1997)], and Bo and colleagues [21]). Because diabetes is associated with comorbid conditions (49, 50), it is encouraging that lifestyle interventions seem to have a positive effect on prevention. Our findings are consistent with those of other reviews that have reported substantial benefit of lifestyle interventions in the prevention of type 2 diabetes (51, 52)" (p.548). <u>Surrogate markers for the development of vascular complications</u> including body composition, metabolic variables (fasting plasma glucose, hemoglobin A1C and lipid levels), blood pressure, physical activity, and dietary nutrient intake: • "In patients who already have type 2 diabetes, there is no evidence of reduced all-cause mortality and insufficient evidence to suggest benefit on cardiovascular and microvascular outcomes" (p.543) • "The strength of evidence is insufficient for the effect of comprehensive lifestyle interventions to prevent CVD events" (p.546) (2 studies 23[Eriksson, 1999],24[Pan, 1997]) • "Overall, the strength of evidence for benefit of lifestyle interventions on retinopathy is insufficient."p546 (24, 32 ie. Da Qing Diabetes Study)

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• "Limitations of this review include low- or insufficient strength evidence for most outcomes across the various interventions. These low grades were driven by high or unclear risk of bias within individual studies (largely due to inability to blind patients in the treatment group), lack of direct evidence for patient-important outcomes, and lack of consistency and precision among studies. There was considerable heterogeneity about dietary and lifestyle interventions. In particular, the third component of the intervention was quite variable, limiting our ability to comment on which additional interventions would be beneficial"(p.549).	• "Most studies reported positive effects for secondary outcomes, including changes in body composition, metabolic variables, physical activity, and dietary intake (**Appendix Table 4**). The results were not always statistically or clinically significant or sustained after the end of the active intervention" (p.546). • Two trials reported on cardiovascular outcomes in high-risk patients, but neither found benefit with lifestyle interventions. This is consistent with the Look AHEAD that involved patients with type 2 diabetes, although it contrasts with the smaller Steno-2 trial" (p.548). <u>Conclusions:</u> • "Although growing evidence shows an additive effect when several risk factors are addressed together (64), we cannot conclusively say that comprehensive lifestyle interventions are better than diet and exercise alone"(p.549). • "Comprehensive lifestyle interventions that include exercise, dietary changes, and at least 1 other component are effective in decreasing the incidence of type 2 diabetes in high-risk patients, and the benefit extends beyond the active intervention phase" (p.549).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			• "Few trials provided data for clinically important outcomes, focusing on surrogate measures for which the clinical relevance is unclear. A further possible limitation includes the group of patients that we identified as being at increased risk for diabetes. This is a controversial area, with various definitions and diagnostic cut points having been proposed over the past few years (65). Finally, we included only RCTs in this review. A systematic review of cohort studies may provide data on the effect of different lifestyle interventions over several years to assess the long-term sustainability and comparative effectiveness of these interventions" (p.549).	

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
Sherifali, 2013 SR Update of 2005 CTFPHC guidelines on screening for T2DM and the evidence review of 2008 USPSFT AMSTAR: 73%	4 UK 1US	**Screening** for T2D Observational study found (Simmons, 2011): examined the impact of early, delayed and no screening for T2D using a 75g OGTT and related cardiovascular (CV) risk factors on mortality. <u>Comparator:</u> No screening	<u>Quality Assessment:</u> • "Individual study quality was assessed as well as overall level of evidence. Study quality was based on the risk of bias due to limitations in design, inconsistency of findings, indirectness, imprecision and publication bias. The strength and quality of evidence was determined based on the GRADE system, using GRADEPro software [10-12]. We abstracted data about the patient population, the study design, analysis and results for each study. Reviews were quality assessed using the AMSTAR tool [13]."p3 <u>Limitations:</u> "This review is not without limitations. The search was limited to only those databases searched in the USPSTF review; therefore EMBASE was excluded. We	See p. 8 for Reliability/Yield of screening tests <u>Overall:</u> • *"Results*: Previous results showing benefit of screening among those with high blood pressure were confirmed. No new or old trials were found regarding the effect of screening for T2DM on mortality, cardiovascular mortality and diabetes related complication outcomes. An observational study demonstrated a modest benefit in mortality in an initial cohort invited for T2DM screening (1990-1992), (HR 0.79; 95% CI 0.63, 1.00), but was not replicated in the second cohort invited for screening (2000-2003). Modeling studies reported that population based screening in high-risk individuals (age and hypertension as risk factors) might increase quality adjusted life years and was cost-effective if screening began at age 45 and every three to five years thereafter. Two new randomized controlled trials noted that screening was associated with higher levels of short-term anxiety and worry, but had limited overall psychological impact" (p.1). <u>*Interpretation*</u>: • This review found no controlled studies of the effectiveness of screening for T2DM, and one observational study demonstrating a modest benefit on mortality. Evidence for the harms associated with screening showed minimal clinical significance. Differences between current and previous evidence can be attributed to the current

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			found no new trials that examined the effectiveness of screening forT2DM. The studies found for the harms (anxiety) of screening were too heterogeneous for a meta-analysis."p11	methodology that integrates the GRADE approach. Recommendations for screening reflect the best available evidence and include screening individuals at high risk for T2DM every 3-5 years with an A1C test, and individuals at very high risk annually with an A1C test."p1 <u>Harms of screening:</u> • "Both studies noted that screening for T2DM in the primary care setting is feasible, may be associated with higher levels of short-term anxiety, and had limited psychological impact [18(Eborall, 2007),19(Park, 2008)]" (p.6). <u>Clinical Effectiveness:</u> • "Since the publication of the 2005 CTFPHC and the 2008 USPSTF report for screening for T2DM recommendations, there has been one new cohort study publication to contribute to the discussion about the effectiveness of screening for T2DM [6,7]. Notably, the previous USPSTF also identified only observational studies and no randomized controlled trials for the effectiveness of screening forT2DM. The population-based study demonstrated that screening had a non-significant reduction on mortality; however, no new evidence was found regarding the effectiveness of screening for T2DM on intermediate outcomes, such as, incidenceofT2DM, differences in A1C levels, and frequency of diagnosis. Notably, the Anglo Danish-

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				Dutch Study of Intensive Treatment in people with screen detected diabetes in primary care (ADDITION) study group focused screening in relatively a low prevalence population (~3%) and only the top quartile of the population at risk were asked to participate in the trial [43,44]" (p.10) ○ Observational cohort study found: "All cause mortality was 21% lower in the cohort that participated in early screening versus not invited to screening (HR 0.79; 95% CI 0.63-1.00); similarly mortality was lower in those with delayed screening (HR 0.52; 95% CI 0.35-0.78) than those not invited to screening [17]" (p.3). <u>Cost-Effectiveness:</u> • "Cost effectiveness studies varied in their conclusions, particularly due to differences in modeling techniques and in assumptions relating to screening methods, glucose control requirements and future treatment protocols. The harms associated with screening for T2DM were minimal, with little effect on anxiety levels, self-rated health status and quality of life. Risk assessment tools with internal and external validity can be effective at identifying individuals who are at high risk of being diagnosed with diabetes. Screening with tests A1C, FPG or OGTT provide similar diagnostic outcomes, however A1C

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				is easiest to administer and is cost effective" (p.11). <u>Recommendations and Conclusions:</u> • "Finally, the CTFPHC recommendations that were generated from this review include the screening of individuals deemed to be at high risk (1/3 or 33% risk of developing T2DM in 10 years) and very high risk (1/2 or 50% risk of developing T2DM in 10 years), as determined with a validated risk calculator, such as the FINDRISC or CANRISK [45]. Specifically, for adults that were at high risk of diabetes, a recommendation to screen every 3-5 years with an A1C test was made and for adults at very high risk, a recommendation of screening annually with an A1C test was stated. Unlike the ADA that states screening should commence at a certain age (45 years) [9], the CTFPHC recommendations relying on calculated risk for T2DM, which considers variables such as age, obesity, history of elevated glucose, history of hypertension, family history of diabetes, limited activity levels and fruit and vegetable intake [45]. The effectiveness of a T2DM screening intervention has not been adequately tested to date in a randomized controlled trial, particularly in individuals at high risk for diabetes and its complications. Screening interventions may include the tests (questionnaire, blood test) or the process (stepwise approach versus an alternative

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				approach). Further research is required to determine the effect of screening forT2DM, the best approach to screening (detection, minimizes harm and is cost effective) and the best treatment once pre-diabetes or T2DM is diagnosed" (p.11).
Shirani, 2013 AMSTAR:36% 9RCTs	6 USA 1 UK 2 Iran	Lifestyle: **Dietary** Approaches to Stop Hypertension (DASH) "encourages the high intake of whole grain, fruits, vegetables, and low-fat dairy products combined with sodium restriction, was originally developed to prevent hypertension. However, it is now recommended as an ideal eating dietary pattern for all adults [7,8]. The DASH diet is high in fiber, antioxidant components, unsaturated fatty acids, and low-fat dairy, which may improve insulin resistance [8,9] and hyperglycemia and lower the risk for type 2 diabetes" (p.939). Comparator: Pre-DASH diet levels of glycemic control	Quality Assessment: • DASH on fasting blood glucose: "Heterogeneity between studies was not significant (Q test, P = 0.4, I^2 = 4.8%)" (p.942) • DASH on HOMA-IR levels: "Heterogeneity between studies was not significant (Q test, P = 0.4, I^2 = 4.8%)" (p.942) • "there was no evidence of publication bias using Egger's test (P for bias = 0.23, 0.39, 0.21, respectively" (p.942) Limitations: "The limitations of this study include varied intervention between clinical trials such as the macronutrient composition of the DASH diet, duration of intervention, and type and detail of the recommendations given. The	Dash on fasting insulin [9(Blumenthal, 2010),11(Lopes, 2003),12(Ard, 2004),16(Lien, 2007),17(Al-Solaiman, 2009),19(Al-Solaiman, 2010),20(Hodson, 2010)] • "meta-analysis showed that diet can significantly reduce fasting insulin concentration, overall (mean difference -0.15; 95% CI, -0.22 to -0.08; P < 0.001). There was no evidence of heterogeneity between the effect size of included studies (Q test, P = 490, I^2 ¼ 0.0%). Although heterogeneity was not found, we categorized studies based on their duration (>or < 8 wk) and included participants (with and without metabolic syndrome and dyslipidemia). Subgroup analysis based on study period showed that the DASH diet can significantly reduce fasting insulin when prescribed for longer than 16 wk (mean difference -0.16; 95% CI -0.23 to -0.08; P < 0.001), whereas the overall effect for studies lasted < 8 wk was not significant (mean difference 0.6; 95% CI -0.25 to 1.45; P = 0.168). Subgroup analysis based on participants' situation showed that the DASH diet can significantly reduce fasting insulin when prescribed for individuals with metabolic syndrome or hyperlipidemia (mean difference -0.16; 95% CI -0.26; -0.05; P < 0.001); whereas the overall effect for otherwise healthy participants

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			DASH diet was not homogeneously prescribed in the different studies. Also, in some studies the DASH diet was part of a lifestyle intervention [12,16,20]. Regarding one of the papers [13] in our meta-analysis, we could not include result from both sexes" (p.946). Strengths: This meta-analysis has some strength, participants were from both sexes, therefore, the difference between the sexes has been considered and the effect of the DASH diet on glycemic control is confirmed in both sexes. In our meta-analysis, six studies were conducted in the United States, one in the United Kingdom, and two in Asia. Therefore, differences in diet in developing countries and Western countries were included in this study" (p.946).	was not significant (mean difference -0.04; 95% CI -0.44 to 0.36; P = 0.831)" (p.942). DASH diet on fasting blood glucose (All RCTs) • "Overall, adherence to the DASH diet was associated with lower FBG levels in two studies [13,21] but the DASH diet did not significantly affect FBG [9,11,12,16,17,19,20]. Overall, the meta-analysis could not show the beneficial effects of the DASH diet on FBG (mean difference -0.26; 95% CI, -0.56 to 0.05; P = 0.1)" (p.942). Effect of the DASH diet on fasting HOMA-IR [11(Lopes, 2003),16(Lien, 2007),17(Al-Solaiman, 2009),19(Al-Solaiman, 2010)] • "None of the studies reported a significant effect of adherence to the DASH diet on HOMA-IR levels compared with the control diet. Overall, meta-analysis could not show the beneficial effect of a DASH diet on HOMA-IR (mean difference -0.26; 95% CI -0.56 to 0.05;P = 0.1). Heterogeneity between studies was not significant (Q test, P = 0.4, I^2 = 4.8%)" (p.942). Conclusions: • "In the present meta-analysis of RCTs, we found that the DASH diet can significantly reduce fasting insulin concentration compared with a control diet. Subgroup analysis based on study period showed a significant effect of adherence to the DASH diet on fasting insulin concentration on

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				longer period of time (>16 wk). It should be noted that with the elimination of the study by Lien et al. [16], a significant relationship between the DASH diet and a reduction in fasting insulin concentration became insignificant. In other words, this association is influenced by a Lien et al. study; therefore, the results should be interpreted with more caution. Our results showed that the DASH diet could not significantly affect FBG. Also the metaanalysis could not show a significant effect of the DASH diet on HOMA-IR levels. Heterogeneity between studies was not significant. In our knowledge, this study is the first systematic review and meta-analysis on the effects of the DASH diet on glycemic control"(p.944). • "The results of the present meta-analysis suggest that the DASH diet can improve insulin sensitivity. The DASH dietary pattern may play a role in glycemic control in long-term interventions. Further prospective studies about the association between the DASH diet and risk factors for type 2 diabetes are necessary" (p.946).
Song, 2012 MA AMSTAR: 36% 11 RCTs	Not reported	**Drug**: "Angiotensin receptor blockers (ARBs), as a new type of antihypertensive agents, enhance insulin sensitivity and therefore benefit patients at high risk of developing type 2 diabetes"p1804	<u>Quality Assessment:</u> • "quality of included randomized controlled trials was assessed using standard criteria (allocation concealment, intention-to-treat	<u>New onset diabetes:</u> • "Overall, there were 3111 new cases of type 2 diabetes (10.7%) in patients treated with ARBs compared with 3685 new cases (12.7%) in subjects treated with placebo or other agents (*OR* 0.8, 95% *CI* (0.76, 0.85)). ARBs were associated with significant reduction in the risk of new-onset type

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		Follow-up: Mean follow up range – 1-4.7years Comparator: Active Control/placebo or usual care	analysis, blinding and completeness of follow-up)"p1805 Limitations: • "First, it should be noted that these are post-hoc analyses of these trials and none of the studies was primarily designed to address the issue of new-onset type 2 diabetes. Second, the variety of methods for the definition of type 2 diabetes between studies. Thirdly, meta-analyses have intrinsic methodological limitations related to combining trials with different designs, treatment strategies, and patient populations. For example, the present analysis combined trials in patients with and without heart failure. Moreover we limited our meta-analysis to studies that evaluated both	2 diabetes in patients with primary hypertension (*OR* 0.75, (0.69, 0.82)), heart failure (*OR* 0.80, (0.64, 0.99)), cardiocerebrovascular diseases (*OR* 0.84, (0.72, 0.97)) or impaired glucose tolerance (*OR* 0.85, (0.78, 0.92)) (Figure 1). There was no heterogeneity and no evidence for publication bias" (p.1806). Incidence of cardiovascular events: • ARBs were not associated with significant reduction in the risk of all-cause death in patients with essential hypertension (*OR* 0.95, (0.87, 1.05)), heart failure (*OR* 0.92, (0.82, 1.04)), cardiocerebrovascular diseases (*OR* 1.04, (0.95, 1.13)) or impaired glucose tolerance (*OR* 0.90, (0.77, 1.06)), when compared with controls (Figure 2). There was low heterogeneity and no evidence for publication bias. • Similarly, ARBs were not associated with significant reduction in the risk of cardiovascular death in patients with essential hypertension (*OR*0.94, (0.84, 1.04)), cardiocerebrovascular diseases (*OR* 0.93, (0.77, 1.12)) or impaired glucose tolerance (*OR* 1.12, (0.87, 1.44)), when compared with controls. Except among patients with heart failure, significant reduction in cardiac death (*OR* 0.88 (0.78, 0.98)) occurred (Figure 3). There was no heterogeneity and no evidence for publication bias.

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			new-onset type 2 diabetes and cardiovascular complication. A number of studies which only evaluated cardiovascular outcomes were excluded, that might have affected the result of ARBs on cardiovascular complications"p1809	The results were similar when ARBs were compared with either placebo or with active treatment for the outcome of myocardial infarction, there were no significant deference occurred in patients with heart failure (*OR* 1.07, (0.75, 1.53)), cardio cerebrovascular diseases (*OR*0.89, (0.71, 1.13)) or impaired glucose tolerance (*OR* 0.99, (0.78, 1.26)), but in patients with primary hypertension, a significantly higher risk of myocardial infarction occurred For the outcome of heart failure, among patients with primary hypertension (*OR* 0.90, (0.80, 1.02)), heart failure (*OR* 0.78, (0.70, 0.87)), cardio cerebrovascular diseases (*OR* 1.04, (0.87, 1.25)) or impaired glucose tolerance (*OR* 0.98, (0.73, 1.31)), respectively (Figure 5). There was moderate heterogeneity and no evidence for publication bias" (p.1806). Conclusions: • "Our meta-analysis provides evidence on the ability of ARBs to reduce the incidence of new-onset type 2 diabetes, when compared to placebo in patients with essential hypertension, impaired glucose tolerance and/or high cardiovascular risk. In this meta-analysis, 58 122 patients without diabetes were evaluated for development of new-onset type 2 diabetes. Pharmacological treatment based on ARBs significantly reduced the odds of new-onset type 2 diabetes compared to control groups. Although we found that ARBs can help to

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				prevent the incidence of new-onset type 2 diabetes in patients with aforementioned diseases. The mechanisms underlying the prevention of new-onset type 2 diabetes by ARBs are complex and not fully elucidated" (p.1807). • "our findings demonstrated that among ARBs trials evaluating new-onset type 2 diabetes, there were no significant differences in all-cause mortality, cardiovascular end points versus control therapy" (p.1808). • "This meta-analysis found that ARBs have significant ability to reduce the incidence of new-onset type 2 diabetes among patients with essential hypertension, cardio cerebrovascular disease, impaired glucose tolerance and heart failure" (p.1809).
Waugh, 2013, HTA Update based on 2 RCTs	Wide range of countries	**Screening** for T2D Wide range of follow-up	No real aggregate data tables since there is limited research to assess.	<u>Overall:</u> "Population screening for T2DM does not meet all of the NSC criteria. Criterion 12, on optimization of existing management, has not been met. A report by the National Audit Office (NAO) gives details of shortcomings. Criterion 13 requires evidence from high-quality randomised controlled trials that screening is beneficial. This has not been met. The Ely trial of screening showed no benefit. The ADDITION trial was not a trial of screening, but showed no benefit in cardiovascular outcomes from intensive management in people with screen-detected T2DM. Criterion 18 on staffing and facilities does not appear to have been met, according to the NAO report. Criterion 19 requires that all other options, including

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				prevention, should have been considered. A large proportion of cases of T2DM could be prevented if people avoided becoming overweight or obese. The first stage of selection would use risk factors, using data held on general practitioner computer systems, using the Q Diabetes Risk Score, or by sending out questionnaires, using the Finnish Diabetes Risk Score (FINDRISC). Those at high risk would have a measure of blood glucose. There is no perfect screening test. Glycated haemoglobin (HbA1c) testing has advantages in not requiring a fasting sample, and because it is a predictor of vascular disease across a wider range than just the diabetic one. However, it lacks sensitivity and would miss some people with diabetes. Absolute values of HbA1c may be more useful as part of overall risk assessment than a dichotomous 'diabetes or not diabetes' diagnosis. The oral glucose tolerance test is more sensitive, but inconvenient, more costly, has imperfect reproducibility and is less popular, meaning that uptake would be lower" (p.v). "Arguments in favour of screening include: • Type 2 diabetes is becoming more common and many people with the condition are undiagnosed. • Health promotion measures to prevent T2DM by persuading people to adopt healthy lifestyles and avoid obesity and overweight have failed. • There have been advances in screening methods, including refinements in risk scoring, and more convenient blood glucose testing using HbA1c levels in non-fasting people.

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				• There have been advances in diabetes care, including retinal screening and a wider range of treatments both for glycaemic control and reduction of cardiovascular risk. So it is more advantageous to be diagnosed than a decade or two ago. • It has been shown, for example, by the ADDITION trial, that people identified by screening to have T2DM or lesser degrees of hyperglycaemia have significant, but treatable, cardiovascular risk factors. Depending on which test is used and what cut-off is chosen, more people with lesser degrees of hyperglycaemia will be found than people with diabetes. NICE has recently issued guidance for this group. • Some people with undiagnosed diabetes will develop retinopathy. Arguments against population screening: • Some of the NSC criteria for a screening programme are not met. In particular, we now have a trial of screening for diabetes but it found no advantage in health measures or cardiovascular morbidity after a 13-year follow-up. • Identifying people at high risk of CVD and applying intensified management, as done in the ADDITION trial, did not result in any benefit. • There is no perfect screening test. The OGTT is inconvenient and time-consuming, requires fasting overnight, and acceptance may be poor.

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				The FPG lacks sensitivity. HbA1c testing costs more than a simple PG test and will miss some people who are identified as diabetic by an OGTT. • If other cardiovascular risk factors are assessed and addressed, the benefits of screening for hyperglycaemia are modest in terms of further reducing cardiovascular risk. • The proportion undiagnosed has probably been reduced by opportunistic screening" (p.xv). "The case for universal screening of those aged > 40 years is not proven. There is a case for selective screening as part of overall vascular risk assessment" (p.xv). <u>Criteria</u> "13. There should be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity. --- Not met The Ely and ADDITION trials showed no benefit in terms of reducing CVD" (p.57). 19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available. ------ Uncertain. In theory, an effective health education campaign to encourage people to keep weight down and take

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				exercise would prevent much of the cases. However, health education appears to be ineffective. Should we try harder? Is there a danger of 'medicalising' unhealthy lifestyles and discouraging people from taking personal responsibility for their own health? "The case for population screening for T2DM remains unproven. It does not meet all of the NSC criteria" (p.65).
Yoon, 2013 SR AMSTAR: 64% 7RCTs	• Indian (1) • Japan(1) • Sweden(1) • Da Quing(3) • SLIM(4) • DPP(5) DPS(10	Lifestyle: Various forms of lifestyle intervention (diet and exercise combo). See table 3 on p309 for details (all **various forms of diet and exercise**) Follow up: range 2.8-6yrs Comparator: All RCTs – control groups	Quality Assessment: • "The reporting quality of each study was assessed by using the CONSORT criteria (Consolidated Standards of Reporting Trials) and the methodological quality by SIGN 50 instrument (Scottish Intercollegiate Guidelines Network methodology checklist for randomized controlled trials)" (p.305). • "To access the reporting quality we used the CONSORT criteria which were primarily designed for randomized controlled trials [69]. The methodological quality	Overall: • "Under consideration of heterogeneity in lifestyle interventions and follow up time of the included studies, this systematic review illustrated that lifestyle intervention can have a beneficial effect on the incidence of diabetes in patients with impaired glucose tolerance. However, several studies found the effect of lifestyle intervention decreased after intervention was terminated. No long-term benefit in mortality and morbidity was found. Development of standardized lifestyle intervention program is strongly needed and further long-term intervention trials using this program are crucial in evidencing the long-term efficacy" (p.304). • "The main finding of this study is that all included studies found a reduction in diabetes type 2 incidence by lifestyle intervention in impaired glucose tolerance patients. The overall incidence of diabetes was reduced by 4% to 21.7% in the intervention group compared with the control group depending on the study and follow-up

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			was determined by SIGN 50 which was described as the best instrument in a Cochrane systematic review [70]. The 10 items which are especially designed for randomized controlled trials, were valid to evaluate the methodological quality of the included studies" (p.311). <u>Strengths</u> • "Strength of our study is that we included the recent data after 2004 using a broader approach to find all available evidence in the literature. We also used a more specific definition of high risk patients" (p.308). • "Additionally, ours is the only study that summarized the different follow-up year analysis results in each study which are important to access the	years. A significant decrease in mortality and morbidity rates was not reported. None of the included studies performed an analysis according to QALY parameters" (p.307). <u>Diabetes Incidence</u> • "Summarizing the result for the primary outcome, most studies found a significant reduction in diabetes incidence through lifestyle intervention. The effect of lifestyle interventions by reducing the diabetes incidence varies from study to study and therefore an interpretation has to be made very carefully" (p.308) (ie. differences in intervention and follow-up time, combined dietary and PS intervention strategies with no clear definitions or standardized protocols, differences in the amount and type of intervention, differences in control groups, variability in included pops, unequal gender distributions in most studies • "the effect of lifestyle intervention decreases as follow-up years increases"p308 "But according to the data, the effect of lifestyle intervention seems to disappear after several years of lifestyle intervention. One possible reason could be that changing lifestyle is very difficult for people. The public's adherence to lifestyle advice and medication varies between 20% and 90%, with most estimates converging around 50% [59,60]" (p.308).

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			long term effect of lifestyle intervention. We believe that our study is a great supplement to the current available evidence" (p.308). • "The strengths of this systematic review are the rigorous methodology, the emphasis on the importance of the clinical questions and the magnitude of the benefits of lifestyle interventions according to evidence level 1" (p.311). • "performed an extended data collection in five different medical related electronic databases" (p.311). • "Also, in order to reduce the selection bias, each identification step was followed by a double data extraction by two independent reviewers. Kappa Cohens showed a range of K=0.77 to	<u>Mortality and Morbidity</u> • "Unfortunately just a few of the included studies conducted some analyses for these parameters. The results of 20-year follow-up analysis of the Da Qing study showed no differences between intervention group and control group in mortality and morbidity. In addition, the Indian study reported no differences in CVD event in intervention and control group" (p.310). <u>Quality adjusted life years</u> • "…none of the included studies performed analysis on QALY" (p.310) <u>Other parameters:</u> • "Overall, we recognized a small benefit of lifestyle interventions in secondary outcome parameters such as BMI and weight change. But all of the results have to be interpreted independently and are not acceptable for evidence" (p.311). <u>Conclusions:</u> • "Consequently, this study added information on how lifestyle intervention produced significant improvement in diabetes incidence but no improvement in mortality, morbidity or other known risk factors for diabetic complications. However, according to the heterogeneity of study designs and multiple influence factors, this study cannot give a definitive answer to the question of whether primary prevention of Type 2 diabetes

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			K=0.81 which means a substantial agreement to almost perfect agreement according to Landis and Koch [71]" (p.311). <u>Limitations:</u> • A potential weakness of this study is that the number of included studies is small and there are no other comparable evidence level 1 studies. Also three of the included studies showed a suboptimal study design with poor methodological quality. Additionally, only half of the studies reported the drop-out rate independently for intervention and control group. Due to the lack of information, attrition bias could influence the results and lead to under or overestimation [72,73]. Moreover, results of our study	reduces the diabetes incidence, but suggestions could be proposed. To clearly confirm the presumption of benefits through lifestyle intervention, standardized definitions and intervention protocols are strongly recommended" (p.312)

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			indicated that researchers frequently fail to provide uniform definitions. For example classification of IGT and diabetes was based on different sources (WHO, ADA) which could influence the incidence [74,75]. Adequate definition of adverse event is essential not only for critical appraisal and interpretation of trial result, but also to facilitate comparison between RCTs, systematic reviews and meta-analysis [76]. Furthermore, individually designed lifestyle intervention programs, which differ in intensity, will probably influence the outcome of the effects. Also the optimum lifestyle intervention has not been defined" (p.312).	

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Yuen, 2010 AMSTAR: 55% 4 RCTs	1 USA 1 Mult sites (Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel, Spain) 1 India 1 China	Lifestyle: (**Diet and Exercise/Weight loss**) and **Medication** interventions Mode of Delivery: • "The intensity, complexity, content and delivery personnel involved in lifestyle interventions differed across studies" (p.174) Medications: • "The medications also varied between studies: three investigated Metformin 16-18 while two acarbose.16,19 Three studies investigated the effects of LSM."p174 • Avg length of studies was 3-5yrs Follow up: Range of follow-up= 2.5-5yrs Comparator: 2/4 Placebo	Quality Assessment: • "…assessed internal validity using The Cochrane Collaboration's tool for assessing risk of bias.14 We only assessed blinding in the medication arms and chose not to consider blinding of outcome assessors" (p.173) • "Meta-analysis was not carried out due to the clinical diversity of trials" (p.173). • "The overall risk of bias was high. Under the category of other sources of bias, two studies terminated early due to treatment effect.17[Ramachandran, 2006],18 [Knowler, 2002] While this risks overestimation of treatment effects, we felt this had minimal impact on the results. In the DPP, the results were unlikely to be a chance finding as the T2DM	Overall: • "There is substantial evidence that intensive lifestyle programs and medications delay T2DM in impaired glucose tolerance though it remains unclear which is more effective"p172 Incidence of T2D • "From these four trials with an overall high risk of bias, it was not possible to draw any firm conclusions on which intervention was more effective in delaying T2DM. It was difficult to directly compare lifestyle and medication interventions in delaying T2DM from the limited studies.16[Fang, 2004), 17[Ramachandran, 2006] We can only speculate that a more intensive lifestyle intervention would be more effective by promoting patient adherence. It could be argued that lifestyle advice given in the IDPP-117 was reinforced more regularly and thus was more likely to change behaviour than that of the Chinese study.16[Fang, 2004] However, the difference between the two interventions was not statistically significant in the IDPP-1.17" (p.175) • "Similarly, results from the limited trials evaluating the effect of LSM versus lifestyle or medication alone seemed to be dependent on the intensity of the lifestyle regime implemented" (p.175). Return to Normal Glucose tolerance:

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			incidence rates were similar at two time points. Furthermore, the results of both trials were not implausibly high compared to a similar trial23 and both trials had a considerable number of participants developing T2DM" (p.174). <u>Limitations:</u> • "…the inclusion criteria of all studies focused on IGT only or IGT with IFG. Therefore, none of the participants had isolated IFG" (p.177) • "…the studies located investigated metformin and acarbose only. Thus, we could not examine the effects of other T2DM drug classes" (p.177) • "We were also unable to adequately investigate the effect of interventions on CVD	• "There were insufficient studies investigating reversion to NGT; most relied heavily on the incidence of T2DM to demonstrate effect. In contrast to reporting changes in glucose concentration, solely reporting T2DM incidence could give healthcare professionals the impression of a greater effect27 and would not allow estimation of the effect on T2DM-related complications.28 Thus, we consider measuring reversion to NGT and glucose concentrations on a continuous scale could aid in result interpretation" (p.175). • "…the inclusion criteria of all studies focused on IGT only or IGT with IFG. Therefore, none of the participants had isolated IFG" (p.175) <u>CVD morbidity and Mortality</u> • "We were also unable to adequately investigate the effect of interventions on CVD morbidity and mortality"(p.176). <u>Medications for T2D</u> • "the studies located investigated metformin and acarbose only. Thus, we could not examine the effects of other T2DM drug classes" (p.176) • "Furthermore, interventions causing substantial side effects would be impractical. Acarbose in particular is of concern as 98% of participants reported adverse events and nearly 15% ceased the medication in the STOP-NIDDM trial,19[Chiasson, 2002] a cessation rate similar to

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			morbidity and mortality" (p.177) • Internal validity and publication bias may be possible in this review • "our requirement for trials to have both lifestyle and medication arms may have limited studies to those with large sample sizes" (p.177) • "the classification of lifestyle interventions was subjective" (p.177) <u>Strengths:</u> • Rigorous methodology • "aimed to keep the review transparent, extensively reporting our methods and results" (p.177) • "articles not limited to English" (p.177) • "Citation bias was also unlikely in this review as three studies [17-19] were retrieved by searching databases and the other [16] was	the Chinese trial.16 As people with prediabetes are often asymptomatic, there is a low threshold for adverse effects. Given the side effects of acarbose were significant enough to affect compliance in a volunteer population, it is not surprising that the American Diabetes Association (ADA) currently considers metformin the only suitable medication for prediabetes.39 However, metformin also demonstrated substantial side effects. The rate of gastrointestinal symptoms in the DPP18 was significantly higher with metformin than with placebo while the side effects in the Chinese study16[Fang, 2004] made three participants stop taking the medication. Twenty-two participants on metformin in the IDPP-117 also reported symptoms of hypoglycaemia. Thus, the future role of medications in prediabetes is uncertain. We are also unsure whether the effects from these interventions last following cessation of active treatment. Both trials with washout periods19[Chiasson, 2002],24 demonstrated a greater incidence of T2DM during the washout period with medication than with placebo thus suggesting medication conceals T2DM via its glucose lowering properties. Therefore to 'prevent' T2DM, lifelong treatment would be required. However, both washout periods were relatively short and therefore it is unclear whether

Citation, AMSTAR score, type & number of included studies	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			retrieved from the reference list of another systematic review, which employed slightly different search filters" (p.177)	cumulative incidence rates would have eventually converged" (p.177). <u>Conclusions:</u> • "The decision whether to implement a lifestyle intervention or begin medication in patients with IGT to delay T2DM should balance the advantages and side effects of each method as well as integrate patients' values. Motivated patients may opt for an intensive lifestyle program with frequent follow-up sessions thereafter due to health benefits beyond lowering their risk of T2DM. The option of metformin could also be discussed though its common gastrointestinal side effects must be considered. The use of acarbose should be precluded by its frequent adverse events. There is currently insufficient evidence to make recommendations in choosing between lifestyle and medication as well as LSM against a lifestyle or medication intervention alone. Furthermore our findings might not be applicable to patients with isolated IFG. We suggest further studies -on more intensive lifestyle modification, incorporating measures to maximise compliance. Future trials should have post-intervention follow-up periods and report glucose measurements on a continuous scale as well as progression to T2DM and NGT" (p.177).

Primary Literature Extraction

Key: Intervention Types

Screening & Lifestyle
Lifestyle: Diet Alone
Lifestyle: PA Alone
Lifestyle: Diet & PA
Lifestyle & Drug
Mixed: Lifestyle/Drugs/Surgery

Table 16: Primary evidence, data extraction

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
Grontved, 2014 **DB: 20/28** Prospective Cohort	United States	**Muscle strengthening and conditioning activities** • "each participant reported her average weekly amount of resistance exercise, lower intensity exercise (yoga, stretching, toning), and aerobic physical activities. There were ten response categories ranging from none to > 11 hours/week activities for these physical activities. Participants were also asked about their usual walking pace (easy <3.2 km/h, normal 3.2–4.6 km/h, brisk 4.7–6.5 km/h, very brisk >6.5 km/h). Aerobic physical activities included brisk walking (for exercise or to work), jogging, running, bicycling, tennis, swimming, other aerobic exercise (aerobic, dance, ski or	Limitations • "the study population consisted of registered nurses with mostly European ancestry. It is therefore unknown if our results can be generalized to other populations of women. **Physical activity was assessed by a self-administered questionnaire and is therefore prone to misclassification**. While our validation study among a random sample n = 147 NHSII participants	Type 2 Diabetes Incidence (difference between baseline and 1yr follow-up) • "We documented 2,158 and 1,333 new cases of T2D during 345,752 and 360,117 person years of follow-up in the NHS and NHSII, respectively" (p.3). • "Participation in muscle-strengthening and conditioning activities was associated with a decreased risk of T2D in multi-variable adjusted analysis, with and without adjustment for aerobic MVPA, in both cohorts of women (Table 2). The

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		stair machine, etc.), daily number of flights of stairs climbed, and other vigorous activities. We considered these aerobic activities of at least moderate intensity (≥3 metabolic equivalent of tasks [METs]) because these activities are usually performed repetitively and produce dynamic contractions of large muscle groups for an extended period of time" (p.2) • "Examples of muscle-strengthening activity include resistance exercise with free weights, weight machines, exercises against own weight, yoga, and outdoor work" • "For each type of activity (aerobic- and muscle strengthening activity), we grouped participants into five categories: none, 1–29 min/week, 30–59 min/week, 60–50 min/week, and more than 150 min/week" (p.2). Follow-up 8years Comparator Baseline cohort info	described a moderate to strong (r = 0.62) relationship between total physical activity as reported in the questionnaire and that reported in four one-week diaries, we did not obtain specific validation data on muscle-strengthening activities, and the validity of the self-reported time spent on these activities remains uncertain in our cohorts. We do not expect differential misclassification of these activities by subsequent incident T2D and the estimated associations of activity with T2D are therefore likely to be underestimated. Because we updated physical activity during follow-up, the expected genuine individual variation in physical activity over time is better accounted for, which would avoid further dilution bias of estimated associations. Furthermore, residual and unknown	pooled RR for T2D for women performing 1–29, 30–59, 60–150, and >150 min/week of muscle-strengthening and conditioning activities was 0.83, 0.93, 0.75, and 0.60 compared with women reporting no muscle strengthening and conditioning activities ($p<0.001$ for trend). When analyzed separately, both resistance exercise and lower intensity muscular conditioning exercise were inversely associated with T2D risk in age-adjusted and multivariable-adjusted analyses in both cohorts. However, when additionally adjusting for aerobic MVPA and mutually adjusting for resistance exercise and lower intensity muscular conditioning exercise, the association was attenuated for lower intensity muscular conditioning exercise in the NHSII, although it was significantly associated with T2D risk in pooled analyses (0.91 [95% CI 0.86–0.96] per 60 min/week of lower

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			confounding cannot be fully excluded, as the present study is observational. As we observed risk reduction with muscle strengthening and conditioning activity among women reporting no aerobic activity, this reassures us that the associations we observed are not likely to be explained by residual confounding by aerobic MVPA" (p.13). <u>Strengths:</u> • "The strengths of the study include the large sample size, updated information on activity and other covariates, and that we were able to control for a wide range of confounding factors. Furthermore, the results were robust to excluding T2Dcases during the first two years of follow-up and using only the baseline information on muscle-strengthening activity" (p.13).	intensity muscular conditioning exercise)" (p.6). • "When we restricted the analyses to women reporting no aerobic activity, engagement in muscle-strengthening and conditioning activity was associated with lower risk of T2D in both cohorts of women (0.85 [95% CI 0.77–0.95] per 60 min/week in the pooled analysis) (Table 3). When we additionally adjusted for BMI, the association of muscle-strengthening and/or conditioning activities with T2D risk persisted (Table 2, model 3). Further adjustment for history of hypertension and raised cholesterol did not materially affect the results in either cohort of women (pooled RR's across categories of muscle-strengthening and conditioning activity were 0.86, 0.94, 0.79, and 0.63 [p<,0.001 for trend]) (Table 4)" (p.6). • "The stratified analyses by BMI indicated that engagement in muscle-strengthening activity was

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				associated with lower T2D risk among overweight (BMI 25 to <30 kg/m^2) and obese (≥30 kg/m^2) women, but no association was observed among normal weight women (BMI <25 kg/m^2) (Table 5). There was no evidence that the association of muscle-strengthening and conditioning activity with T2D risk was different across age (<65, ≥65 years, NHS only), family history of T2D, diet quality score, race (white, non-white), and aerobic MVPA (quintiles) in either cohort of women (p>0.05 for multiplicative interaction) (Table S3). Aerobic MVPA was inversely associated with T2D risk in the multivariable model after adjustment for resistance exercise, lower intensity muscular conditioning exercise, and BMI in both cohorts (p>0.001 for trend) (Table 6). Spline regression revealed that the association of aerobic MVPA with the risk T2D was non-linear in both cohorts, with the steepest gradient at lower

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				levels of activity (p<0.01) (Figures S1 and S2). Achievement of recommendations [13–15] for muscle-strengthening and conditioning activities (none/no/yes) and aerobic MVPA (none/no/yes) was each independently associated with lower T2D risk in multivariable adjusted analysis: the pooled RR was 0.46 (95% CI 0.41–0.50) for aerobic MVPA and 0.72 (95% CI 0.65–0.79) for muscle-strengthening and conditioning activities compared with women reporting no activity (Figure 7). Furthermore, compared with women reporting no activity, engagement in a level of activity that is less than the recommended, of either muscle-strengthening type or aerobic MVPA, was associated with a lower T2D risk (pooled RR=0.72 (95%CI 0.66–0.78) for aerobic MVPA and pooled RR=0.87 (95% CI 0.80–0.95) for muscle strengthening and conditioning activities). In the joint association analysis,

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				women who adhered to the recommendations for both aerobic MVPA and resistance exercise had the lowest risk of T2D risk in the multivariable model, with a pooled RR of 0.33 (95% CI 0.29–0.38) compared with women who were inactive (Table 7)." • "We found that adiposity indicated by BMI only partly explained the association of muscle-strengthening and conditioning activities with T2D risk, suggesting that participation in these types of activities can lower T2D risk without changing body weight. However, BMI is unable to distinguish fat mass from fat-free mass, and engagement in muscle strengthening activity is likely to increase fat-free mass while decreasing fat mass. We also observed greater risk reduction with participation in muscle-strengthening and conditioning activity among overweight and obese women and no apparent effect among normal weight women. This may suggest that these types

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				of activities have less effect in terms of T2D prevention among women who already maintain a healthy weight" (p.12). <u>Conclusions:</u> • "this large prospective study of US women suggests that engagement in muscle-strengthening and conditioning activities can lower the risk of T2D independent of aerobic MVPA. Following the recommendations for both muscle-strengthening activities and aerobic MVPA was associated with a substantial reduction in the risk of T2D. Engagement in levels lower than currently recommended of aerobic physical activity and muscle-strengthening and conditioning activity were also significantly associated with lower T2D risk. Collectively, our study supports the inclusion of muscle-strengthening and conditioning activities in preventive measures against T2D, consistent with the

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				current guidelines for physical activity among adults" (p.13).
Hellgren, 2013 **DB=20/28** Randomized clinical trial	Gothenburg, Sweden	**<u>Program focused on physical activity for diabetes prevention</u>** performed over one year intended for an intention-to-treat analysis). **1) Basic intervention group** • "Care as usual • Card giving them possibility to take their blood glucose freely • Personal nurse to contact when needed • Prescription for physical activity • A step counter"p465 2) **Intensive intervention group.** • "As the basic intervention group plus an invitation to participate in eight group sessions focusing on physical activity (six sessions the first six months and another two sessions the following six months). A lifestyle coach (nurse), a nutritionist and a physiotherapist chaired these sessions. The sessions were solely focused on physical activity and were held daytime" (p.465). Follow-up: 1 year <u>Comparator:</u> Care as usual: "Information on IGT was given orally and in writing. Brochures with information about diet and physical activity were distributed. The participants were informed that a new	<u>Stats</u> • SPSS program • Paired samples T-test • Baseline variables analysed with ANOVA and Chi^2 test • All analyses adjusted for differences in age and gender and 2-sided 95% confidence intervals were presented ($p<0.05$) <u>Strengths:</u> • "The strength of the study is that it is tested and implemented in ordinary primary care with resources available in everyday practice" (p.468). <u>Limitations:</u> • "…was the limited number of participants. For a full scale study a careful power calculation based on experiences from the pilot study will be necessary. Another limitation was the unexpected difficulty in conducting a reliable test of VO2max. The bicycle test according to Åstrand	<u>Physical Activity and Fitness:</u> • "Because of the high comorbidity, only 33 (75%) of the study participants could complete the bicycle test" (p.467). • "In the interview 69% of the participants in the intensive care group reported a considerable increase in their physical activity (5 or 6 on a 6-grade scale), while 17% in the basic group and 44% in the control group reported an equal increase. Mean increase in the different groups was 3.0, 2.8 and 3.8, in the control group, the basic care group and the intensive intervention group respectively, with no statistical difference between them (p=0.137). Most participants reported an increase in walking or biking. Participation rate in the group sessions was high, 53% attended all the sessions and 80% participated in seven of eight sessions, only three participants attended three times or less. Interestingly,

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		examination would take place after one year" (p.465).	proved to be difficult to perform and Downloaded from not reliable in this particular sample of elderly participants. However, the novelty of this study is the unexpected high comorbidity of individuals recruited by FINDRISC and the additive effect on diet in a programme focused on isolated physical activity " (p.468).	60% of the participants reported some changes in diet"(p.466). <u>Intra-individual changes at one-yr follow-up:</u> • "Of the 52 individuals included at baseline, six participants progressed to diabetes (12%) during the first year, two in the intensive care group, one in the basic care group and three among those allocated to care as usual. Data below refer to those with complete data at the one-year follow-up. Risk factors for ischaemic heart disease, like systolic and diastolic blood pressure (12 mmHg, *p*=0.003, CI 5.0–19.3; 7 mmHg, *p*=0.005, CI 2.4–11.0), weight (3 kg, *p*=0.017, CI 0.6–5.5), BMI (1 kg/m2, *p*=0.013, CI 0.3–5.5), waist circumference (3 cm, *p*=0.026, CI 0.4–5.6) and sagittal diameter (1.2 cm, *p*=0.028, CI 0.1–2.3) decreased significantly within individuals in the intensive care group, and systolic blood pressure (8 mmHg, *p*=0.025, CI 1.4–18.4) decreased in the basic

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				intervention group. No other differences were significant (data not shown)" (p.467). <u>Differences between groups:</u> • "Weight, BMI, waist circumference and sagittal diameter were significantly more reduced in the intensive care group compared with the control group and the basic care group The difference was significant for waist circumference and sagittal diameter when comparing intensive and care as usual and for weight and BMI when comparing the intensive and the basic care group, adjusted for differences in age and sex. However, when adjusted also for energy intake this difference was abolished. No conclusive effect could be reported from the bicycle test. Complete data were reported for 45 individuals (Table III)" (p.467). <u>Main findings:</u> • "…first, that individuals recruited by the FINDRISC questionnaire had very high

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				comorbidity. Secondly, an intervention with a focus on physical activity implemented changes in diet. Third, it took more than just an examination, a prescription of physical activity and a step counter to increase physical activity over time (one year) and, fourth, a lifestyle intervention is applicable in ordinary primary care with limited resources, and can influence severe risk factors for cardiovascular disease" (p.467). <u>Conclusions:</u> • "We found that an intervention aiming at an increase in physical activity in ordinary primary care was feasible and that the induced lifestyle changes in an intention-to-treat perspective were efficient in spite of high comorbidity in the study group. In addition we also found that an intervention with isolated focus on physical activity implemented dietary changes" (p.469).

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Lian, 2014 **DB=25/28** Double-Blind, Randomized , Placebo Controlled parallel group, multicenter trial	China Multisite	**<u>Lifestyle intervention plus Tianqi capsules</u>:** • Run in Period: "Dietary education consisted of advice on maintaining a balanced and reasonable diet. The intervention education included two face-to-face counseling sessions with certified nutritionists. The daily caloric requirements were calculated based on the individual subject's height, weight, and physical activities. A daily diet was selected based on clinical nutritional requirements using the Chinese Food Composition Table or Food Serving Exchange Table. The subjects were also asked to maintain their usual patterns of physical exercise and to continue normal daily lifestyles throughout the trial. Additional counseling sessions were held at 3 months, 6 months, and 9 months to ascertain that subjects followed the lifestyle guidance, or the subject would be excluded from the study" (p.650). • "The Tianqi capsules, manufactured by Heilongjiang Baoquan Pharmaceutical Co, were used. The placebo, which contained sugar-free starch and medicinal yellow iron oxide, was also supplied by the same manufacturer. The color, odor, shape, and packaging of the placebo capsules were exactly the same as those of the Tianqi capsules" (p.650). • "Subjects in both the Tianqi and placebo groups were orally administered five	<u>Quality:</u> Randomization and blinding: • "A stratified, block randomization method was conducted by the study center. Study drugs were packed and numbered according to the random coding form and randomly allocated to each research site using concealed opaque envelopes. These envelopes and case report forms were not collected until the end of the trial. Study drugs were provided based on the assigned numbers, which were determined according to the visit sequence and study drug number sequence, and remained unchanged throughout the trial. Independent statisticians performed the data analysis (Peking University Health Science Center and China-Japan Friendship Hospital, China)" (p.651). • "Of the 420 subjects with IGT who entered the randomization, 389	<u>Progression of IGT to T2DM over 12 mons</u> • "At the end of the 12-month trial, 36 subjects in the Tianqi group (18.18%) and 56 in the placebo group (29.32%) had developed diabetes (*P* = .01). There was a significant difference in the number of subjects who had NGT at the end of the study between the Tianqi and placebo groups (n = 125, 63.13%, and n = 89, 46.60%, respectively; *P* = .001) (Figure 1A). The annual incidence of diabetes was 283.68 per 1000 person-years in the Tianqi group vs 424.72 per 1000 person-years in the placebo group. The Cox's proportional hazards model analysis showed that Tianqi reduced the risk of diabetes by 32.1% compared with the placebo (hazard ratio 0.679; 95%confidence interval 0.471–0.979), after adjusting for age and sex (Figure 3)" (p.652). • "At the end of the 12-month trial, the number of subjects who had developed diabetes between the Tianqi and placebo groups, in range

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		capsules (1.6 g) three times daily before each meal" (p.651). • "The Tianqi or placebo treatment lasted 12 months. During this 12-month period, subjects were assessed every 3 months by undergoing a standard 75-g OGTT" (p.651). Follow-up: 1 year **Comparator:** <u>Placebo</u> • "Subjects in both the Tianqi and placebo groups were orally administered five capsules (1.6 g) three times daily before each meal" (p.651). • Over 12 mon period	subjects completed the study including 198 in the Tianqi group and 191 in the placebo group. The remaining 31 subjects (n12 in the Tianqi group and n=19 in the placebo group) dropped out of the study, mainly due to lack of follow-up, and one subject per group had mild adverse reactions (Figure 1)" (p.652). <u>Baseline Characteristics:</u> • "The mean BMI in both the Tianqi and placebo groups was 25 kg/m2. More than half of the subjects had elevated triglyceride, total cholesterol, and LDL levels, whereas their BP was in the normal range. There were no significant differences at baseline in subjects' age, gender, FPG, 2-hour plasma glucose, lipid levels, BP, heart rate, BMI, and waist circumference between the two groups" (p.652). <u>Limitations</u>:	(mean), was 13.79%–25.00% (18.18%) and 26.67%–35.71% (29.32%), respectively. In addition, the number of subjects who had NGT at the end of the study between the Tianqi and placebo groups was 56.25%–68.97% (63.13%) and 42.80%–50.00% (46.60%), respectively" (p.653). • "…when the last subject completed the study, 50 subjects in the Tianqi group (25.25%) and 67 in the placebo group (35.08%) still remained diabetic (P .035). However, there were 71 subjects in the Tianqi group (35.68%) and 71 in the placebo group (37.17%) who remained in NGT (P .7878)" (p.653) <u>Body weight &BMI</u> • "At 0, 6, and 12 months, the body weight in the Tianqi group (n = 198) and the placebo group (n = 191) were 67.86 +/- 9.94, 67.69 +/- 10.24, and 67.6 +/-10.18 kg and 69.26 +/- 10.31, 69.04 +/- 9.85, and 69.17 +/- 9.78 kg, respectively. At 0, 6, and 12

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			• "…the 12-month study period, which was relatively short. Due to limited research funding availability, plasma insulin levels and HbA1c were not able to be measured. Our data require further verification in interventional studies with a larger sample size and longer length of treatment and follow-up" (p.654).	months, the BMI in the Tianqi group (n = 198) and the placebo group (n = 191) were 25.13 +/- 3.02, 25.04 +/- 3.00, and 25.01 +/- 2.96 and 25.52 +/- 2.64, 25.45 +/- 2.72, and 25.5 +/- 2.70, respectively. There were no statistical differences in body weight and BMI changes between the two groups at any of these time points" (p.653). • "We observed that the Chinese herbal formulation Tianqi effectively delayed the progression from IGT to diabetes. The overall reduction in risk for diabetes over 12 months was 32.1%, which was less than that achieved by rosiglitazone in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication study (62%) (24, 27) and pioglitazone (72%) (28), but it was similar to that achieved by acarbose (25%) (29) and metformin (31%) (17, 30, 31). Our data also showed that after a period of cessation of the Tianqi treatment, the preventive effects on T2DM

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				development remained significant" (p.654). Safety and Adverse events: • "26 subjects in total (15 in the Tianqi group and 11 in the placebo group) experienced adverse events, all of which were mild adverse reactions (grades 1–2). Gastrointestinal reactions, such as nausea, flatulence, constipation, and diarrhea, were the most common. These gastrointestinal events occurred in 15 subjects (n = 6 in Tianqi group and n = 9 in placebo group). In addition, in the Tianqi group, one subject experienced a skin rash and another subject experienced tinnitus. In the placebo group one subject experienced genital swelling and another subject experienced elevated urinary protein (Table 2). No severe adverse events occurred in the trial" (p.653). Conclusions: • "In summary, the Tianqi capsule effectively reduced the incidence of diabetes in

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				Chinese prediabetes subjects with IGT. This Chinese herbal medicine may help prevent diabetes in individuals who are at high risk of developing T2DM" (p.654).
Long, 2014 **DB=23/28** Data from cluster randomized trial	"49 general practices (GPs) in eastern England were cluster randomized to screening, followed by IT (n = 26) or RC (n = 23)"p1713	**Intensive multifactorial treatment (IT)** • "…received theory-based health promotion materials concerning diet, physical activity, tobacco use, and medication adherence. Practitioners in the IT group were encouraged to follow a stepwise target-led treatment regimen to reduce and control CVD risk factors, including blood glucose level, blood pressure, and lipids levels (17,20)."p1713 • Diabetes was diagnosed according to World Health Organization criteria • Used the Cambridge Diabetes Risk Score Follow- up: interquartile range was 5 years (1.3 years; 4361 person-years at risk) <u>Comparator:</u> Routine care "…followed U.K. national guidelines for diabetes management" (p.1713)	<u>Quality:</u> • "All primary end-point events of interest were independently adjudicated by two experts, who were unaware of group allocation, according to an agreed protocol using standardized case report forms" (p.1713). • Compared with those who had complete health behavior data, participants with missing data were more likely to have a lower socioeconomic status (social class: $x_2^6 = 18.9$, $P \leq 0.001$; occupation: $x_2^6 = 16.5$, $P = 0.01$), but were similar with respect to other baseline variables ($P = 0.05$, data not shown). The hazard ratios for risk of composite CVD outcome from analyses with imputed missing health behavior and drug	<u>Health behaviors and CVD risk factors (between baseline and 1yr)</u> • "Between baseline and 1 year, improvements were seen in the majority of health behaviors and CVD risk factors across study groups, including significant reductions in alcohol intake, total energy, and fat intake, and reductions in BMI, mean cholesterol, and HbA1c levels in both men and women (Table 1). Ten people experienced a CVD event before the 1-year follow-up, and 2 people withdrew from the study, leaving a total of 855 participants for analysis. The median follow-up time (inter quartile range) was 5.0years (1.3years; 4,361 person-years at risk), during which time 6% of the cohort experienced a composite primary CVD event (53 of 855 participants), corresponding to an incidence rate of 12.2

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			prescription data differed by an average of 10% (range 3–22%) from those obtained with original list-wise deleted models (Supplementary Table 1). Sensitivity analyses omitting revascularization from the composite CVD end point (n = 18), omitting abstainers (n = 173), and using the ratio of polyunsaturated to saturated fat rather than the percentage of energy from total fat did not qualitatively change these results (data not shown)" (p.1717). <u>Strengths</u> • "We recruited participants from a large, population-based sample, covering an extensive geographical area in the East Anglia region of the U.K., ensuring generalizability to similar settings. The study population exhibited socioeconomic, but not ethnic, diversity. The duration of follow-up,	per 1,000 person years (95% CI 9.3–15.9). The CVD events comprised 21% of CVD deaths (11 deaths), 23% of myocardial infarctions (12 infarctions), 23% of strokes (12 strokes), and 34% of revascularizations (18 revascularizations)" (p.1714). • "…alcohol consumption was the only health behavior that was independently associated with CVD incidence over 5 years, adjusting for age and sex. Individuals who continued to drink alcohol, or who increased their consumption in the year after diagnosis, had a higher rate of CVD than those who abstained or reduced their alcohol consumption. Additionally adjusting for social class and occupation, and mutually adjusting for changes in other health behaviors strengthened the association between change in physical activity, alcohol intake, and CVD risk. Individuals who increased their physical activity levels, or abstained or reduced their alcohol intake, had a lower

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			repeat measurement of lifestyle behaviors, and high participant retention (93% of those alive at 1 year) allowed us to quantify the effects of behavior change early in the diabetes trajectory. We achieved 99.8% end-point ascertainment, and all end points were independently adjudicated. Results from a number of sensitivity analyses, including those imputing missing data, were qualitatively the same as those from the complete case analyses, supporting the robustness of our estimates. Baseline CVD risk factor levels did not differ significantly between categories of health behavior score, suggesting that the benefit of behavior change was not attributable to pre-existing characteristics of participants. Use of self-reported physical activity, dietary, and alcohol data could introduce some measurement error and	CVD risk compared with those who decreased their activity levels (RR 0.53; 95% CI 0.29–0.96) or who consistently drank or increased their alcohol consumption (RR 0.40; 95% CI 0.21–0.78), respectively. Further adjustment for the prescription of cardio protective medication did not attenuate the association between changes in physical activity, alcohol consumption, and CVD events (Table 2). Including baseline BMI in the final model decreased the RR for the association between change in alcohol consumption, and physical activity and CVD risk (by 9% and 7%, respectively), but did not alter the statistical significance of the association between health behavior change and CVD risk. A similar decrease in the RR for the association between change in alcohol consumption, and physical activity and CVD risk was observed once baseline waist circumference was included in the final model

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			bias. However, we used previously validated questionnaires (22,23), and much error, if introduced, is likely to underestimate the strength of the association. Furthermore, given the reliability of the measures, repeat use of the same instruments should reduce bias and allow changes in behavior to be quantified (39)" (p.1718). Limitations: • "Smoking status is a well-known modifiable risk factor for early death (40), but the low number of patients who reported smoking cessation between baseline and 1 year (n = 15) precluded analysis of the impact of a change in smoking status on 5-year CVD risk" (p.1718). • "Dichotomizing change in healthy behaviors into individuals who increased or decreased their behaviors ensured an adequate number of	(4% decrease in both cases), but did not qualitatively alter the association between health behavior change and CVD risk. These reductions in RR suggest that changes in body composition may, at least in part, mediate the association between behavior change and CVD risk. There was a significant inverse association between the health behavior change score and incident CVD events (Table 3 and Fig. 1). Only 20 people changed all health behaviors, so individuals with a health behavior change score of three or four were combined in these analyses. Participants who improved three or four health behaviors (n = 176 of 600 participants, 30%) had the lowest rate of CVD events. Participants who did not change any health behaviors (n = 37 of 600 participants, 6%) had a 3.71 times higher CVD event rate (95% CI 1.02– 13.56, P for trend = 0.03), and this association remained significant after adjusting for

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			events and sample sizes for all analyses, but could exaggerate the magnitude of associations and obscure the gradient of association between behavior change and CVD risk. The low number of events and the potential for differential measurement error in the self-reported behaviors also precluded us from a detailed quantification of the magnitude of behavior change needed to reduce CVD risk. However, we highlight that there was a clear separation of the CVD survival curves, even with our relatively crude measure of behavior change, supporting our interpretation of the findings" (p.1718).	prescription of antihypertensive, glucose-lowering, and lipid-lowering medication (P for trend = 0.04). CVD events occurred more often in men than in women (44 of 53 CVD events in men, 83%), which prevented examination of a differential effect of health behavior change on CVD risk by sex. Assuming the association between unhealthy behavior and CVD outcome is causal, 50.2% (95% CI 4.9–76.4%) of CVD events in this population could be attributed to not changing three of four health behaviors in the year after diabetes diagnosis, and 35.4% (95% CI 0.44–58.1%) of CVD events could be attributed to not changing two health behaviors (the population attributable fraction for CVD)" (p.1716). <u>Conclusions:</u> • "Patients with newly diagnosed type 2 diabetes who increased their physical activity levels and abstained or reduced their alcohol intake in

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				the year after diagnosis of diabetes had a lower risk of CVD events over 5 years compared with individuals who did not change their behavior. The association between modifying these health behaviors early in the disease trajectory and reduced CVD risk were independent of age, sex, study group, social class, occupation, and the prescription of cardioprotective medication. The greater the number of healthy behavior changes made in the year after diabetes diagnosis, the lower the CVD risk. We demonstrate that the association between health behavior change and reduced CVD risk is likely, in part, mediated through changes in body composition" (p.1717). • "Early improvements in health behaviors in the ADDITION-Cambridge cohort were associated with a reduction in incident CVD over 5 years, emphasizing the importance for practitioners to encourage healthy behavior change

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				immediately after diagnosis. Our findings suggest that the biggest effects on CVD risk came from changes in physical activity and alcohol consumption, rather than diet" (p.1717). • "This is the first study to show that healthy behavior changes in the year after diagnosis of diabetes are associated with significant reductions in the risk of incident CVD over 5 years, independent of cardioprotective medication use. Our results suggest that a combined approach that includes early improvements in health behaviors and cardioprotective medications is a beneficial strategy for reducing long-term CVD risk. The year after diagnosis of diabetes is an important period for encouraging change, and maintaining healthy behaviors and habit formation, which should continue to be a major focus for practitioners. How best to help patients achieve and maintain these changes remains uncertain, and should

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				be the focus of future research"(p.1718).
Salas-Salvado, 2014 **DB: 22/28** Subgroup analysis of a multicenter trial (parallel-group, randomized, primary cardiovascular prevention)	Primary care centers in Spain	**1 of 3 Diet interventions**: 1. Mediterranean diet supplemented with extra-virgin olive oil (EVOO), 2. Mediterranean diet supplemented with mixed nuts, 3. or a control diet consisting of advice to reduce intake of all types of fat Intervention Description: • "A behavioral intervention promoting the Mediterranean diet was implemented in the corresponding groups of the trial, as described (13). Dietitians gave personalized advice to participants about the amount and use of EVOO for cooking and dressing; weekly intake of nuts; increased consumption of vegetables, fruits, legumes, and fish; recommended intake of white meat instead of red or processed meat; avoidance of butter, fast food, sweets, pastries, or sugar-sweetened beverages; and the dressing of dishes with "sofrito" sauce (using tomato, garlic, onion, and spices simmered in olive oil). Reduction of alcoholic beverages other than wine was advised to all participants. Wine with meals was recommended with moderation only to habitual drinkers At baseline and quarterly thereafter, dietitians conducted individual and group	Quality: • "computer-generated random numbers for allocation contained in sealed envelopes, which were centrally prepared for each center by the coordinating unit. Four strata of randomization were built by sex and age (cutoff, 70 years) but not by baseline diabetes status. The primary care physicians did not participate in the randomization process. The study nurses were independent of the nursing staff of the primary care health centers. Therefore, they were not involved in the usual clinical care of participants, and their exclusive role was to collect data for the trial. Given the nature of the interventions (nutritional advice and provision of foods), only investigators assessing outcomes were blinded with respect to	Diabetes incidence (follow- up = 4yrs (median), interquartile range, 2.5 to 5.7 years) • "During follow-up, 80, 92, and 101 new-onset cases of diabetes occurred in the Mediterranean diet supplemented with EVOO, Mediterranean diet supplemented with mixed nuts, and control diet groups, respectively, corresponding to rates of 16.0, 18.7, and 23.6 cases per 1000 person-years. Multivariate-adjusted hazard ratios were 0.60 (95% CI, 0.43 to 0.85) for the Mediterranean diet supplemented with EVOO and 0.82 (CI, 0.61 to 1.10) for the Mediterranean diet supplemented with nuts compared with the control diet" (p.1). • "We found that a long-term intervention with a high-quality dietary pattern akin to the traditional Mediterranean diet and rich in EVOO could reduce the incidence of diabetes in older persons at high cardiovascular risk. This

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		dietary training sessions to provide information on typical Mediterranean foods, seasonal shopping lists, meal plans, and recipes for each group. In each session, a l4-item questionnaire was used to assess adherence to the Mediterranean diet (13, 14) so that personalized advice could be provided to upgrade participants' adherence" (p.2). • "Participants assigned to the 2 Mediterranean diet groups received allotments of either EVOO (50 mL/d) or mixed nuts (30 g/d: 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts) at no cost" (p.2). <u>Measurements:</u> • "…137-item validated semi quantitative food-frequency questionnaire (19); the validated Spanish version of the Minnesota Leisure-time Physical Activity Questionnaire (20); and a 47-item questionnaire about education, lifestyle, medical history, and medication use" (p.3) • Blood pressure • Fasting blood • Spot urine • Serum glucose, cholesterol and triglycerides levels	intervention assignment. This was done by providing them with coded data sets and medical records blinded with respect to the personal identity of the participant and without any information on treatment allocation."p2 • "Laboratory technicians were blinded to intervention group."p4 • "A total of 252 participants had been lost to follow-up for 2 or more years (4.1% in the Mediterranean diet supplemented with EVOO group, 6.9% in the Mediterranean diet supplemented with mixed nuts group, and 10.5% in the control diet group). Compared with participants who remained in the trial, those who withdrew were younger (by 1.0 year) and had a greater body mass index (by 0.5 kg/m^), greater waist circumference (by 2.7 cm), and lower adherence to the Mediterranean diet (by 0.44 points in a range	beneficial effect was mainly due to the overall composition of the dietary pattern, and not to calorie restriction, increased physical activity, or weight loss because such lifestyle changes were not part of the intervention and between-group changes were negligible. After a median 4.1-year follow-up, a statistically significant 40% relative risk reduction and a nonsignificant 18% risk reduction in diabetes risk was seen in the Mediterranean diet groups supplemented with EVOO and mixed nuts, respectively, in comparison with the control diet group"(p.8). • "…the 2 Mediterranean diet groups, but not the control diet group, increased adherence to the Mediterranean diet, as assessed by the l4-item Mediterranean diet screener. In fact, we saw better achievements in 9 of the 14 items of the questionnaire measuring adherence to the Mediterranean diet among persons in both

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		Follow-up = after 4yrs (median), interquartile range, 2.5 to 5.7 years <u>Comparator</u>: **Control diet = advice to reduce intake of all types of fat** • "The same questionnaire was assessed yearly in the control group [as the intervention arms]" (p.2). • "Participants assigned to the control diet received recommendations to reduce intake of all types of fat (from both animal and vegetable sources) and received nonfood gifts (kitchenware, tableware, aprons, or shopping bags). Through October 2006, participants in the control group received only a leaflet describing the low-fat diet" (p.2). Thereafter, participants assigned to the control diet also received personalized advice and were invited to group sessions with the same frequency and intensity as those in the Mediterranean diet groups. A separate 9-item dietary questionnaire (14) was used to assess adherence to the low-fat diet. Neither energy restriction nor increased physical activity was advised for any intervention group" (p.3).	of 0 to 14) (P< 0.050 for all comparisons). Clinical characteristics at baseline by study group were similar"p5 <u>Limitations</u> • "First, diabetes incidence was a secondary end point, not the primary end point of the PREDIMED trial, and this was a secondary analysis conducted in the subgroup of persons without diabetes, making these analyses exploratory in nature. However, there are no reasons to believe that the randomization would not have worked in such a large subset of participants. Second, the study sample consisted of older white persons at high risk for coronary heart disease, which limits the generalizability of our results to other age groups or ethnicities. Third, we had greater losses during follow-up in the control group, but participants who withdrew had a worse	Mediterranean diet groups than in the control group. Therefore, the PREDIMED interventions resulted in differences in the overall dietary pattern between the Mediterranean diet and control groups. These differences were probably critical to the dissimilar rates of incident diabetes seen by treatment allocation. In a previous single-center"(p.8). <u>Conclusions:</u> • "…the PREDIMED trial provides strong evidence that long-term adherence to a Mediterranean diet supplemented with EVOO without energy restrictions, which is high in monounsaturated fat and bioactive polyphenols, results in a substantial reduction in the risk for type 2 diabetes among older persons with high cardiovascular risk. Of note, this dietary pattern is palatable and has a high potential for long-term sustainability, with obvious public health implications for

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			cardiovascular risk profile at baseline than those who remained in the study, suggesting a bias toward benefit in the control group. Fourth, participants and study personnel were aware of group allocation because blinding is rarely feasible in feeding trials, but new-onset diabetes was ascertained by PREDIMED medical investigators and confirmed by the adjudication committee, and both were blinded to the intervention. Finally, we cannot discard measurement errors affecting physical activity and alcohol intake during follow-up."p8 <u>Strengths</u> • "The study also has strengths, such as its randomized design, which resulted in treatment groups being well balanced for potential sources of confounding and being able to provide first-line	primary prevention of diabetes" (p.8).

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			evidence to support a causal association. This is a considerable advantage over previous studies assessing the association between high-quality dietary scores and diabetes incidence used in observational designs. Other strengths include the relatively long followup, control for many potential confounding variables, and inclusion of sensitivity analyses" (p.8).	
Tokunaga-Nakawatase, 2014 **DB= 24/28** Two- arm, randomized controlled trial that was a part of a 3 armed, an unmasked, randomized longitudinal trial at a single medical check-up center	Tokyo, at a single metropolitan medical check-up centre	**Lifestyle Intervention Support Soft-ware** • Authors developed Lifestyle Intervention Support Soft- ware for Diabetes Prevention LISS-DP can easily provide education regarding the incorporation of healthy dietary and physical activity behavior into participants' daily life by indirect intervention. Description: "Participants in the LI[Lifestyle Intervention] group received indirect lifestyle intervention supported by LISS-DP three times over a period of six months Lifestyle intervention in this study featured tailored, concrete lifestyle recommendations in a computer- based, non-face-to-face format using LISS-DP. The contents of LISS-DP were developed by the	Quality • "…participants were randomly allocated to the group of indirect lifestyle intervention supported by LISS-DP (LI group) or the control group" (p.209). • "A total of 47 (74.6%) participants in the LI group and 50 (87.7%) in the control group completed the one-year survey. For secondary outcome, biomedical data were obtained from46 (73.0%) in the LI group and 35 (64.8%) in the control group who had under- gone an annual	Changes in total Energy intake between baseline and the end of the intervention period (ie. baseline – 6 months, final follow up at 12 mons) • "…there was a significant difference in total energy intake between the two groups at baseline. The change in energy intake from baseline to six months among subjects in the LI group was significantly greater than that among those in the control group (−118.31 and −24.79 kcal/day, respectively, p = 0.0099, Cohen's d = 0.22). A difference in change in energy

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
		authors based on a lifestyle intervention protocol for secondary or tertiary prevention in type 2 diabetes patients [30–33]. The intervention strategy consists of the following processes: (1) lifestyle and background data collection byself-administered questionnaire; (2) generation of tailored recommendations; (3)output of tailored recommendations ;and(4) delivery of the recommendations via mail. Both groups received pamphlet about general information on diabetes prevention with regard to favorable behavior related to diet and physical activity" (p.209). "The periods of follow up were from May 2010 to September 2011" (p.209). <u>Comparator:</u> "Both groups received pamphlet about general information on diabetes prevention with regard to favorable behavior related to diet and physical activity. Participants allocated to the control group received conventional routine care during the study period and indirect lifestyle intervention supported by LISS-DP after the end of study period" (p.209).	medical checkup at the same hospital 1 year after baseline. There was no difference in background characteristics and biomedical data at baseline between the two groups" (p.209). <u>Limitations</u> • "…the overall acceptance rate in this trial was 40.1% (216 of 538 eligible examinees). This low acceptance rate involves a sampling bias, but it is unclear whether the bias led to under- or overestimation of the results. However, the acceptance rate in the present study was remarkably higher than in similar previous studies, which reported an acceptance rate of 5% [43] to 10% [42]. Second, this study was conducted at a single medical check-up center in an urban area of Tokyo, and most of the examinees were employees. This may also	intake between subjects in the LI group and those in the control group was not shown at three months (22.90and −7.40 kcal/day, respectively, p = 0.9981, Cohen's d =−0.07), and 12 months (−13.13 and−75.09 kcal/day, respectively, p = 0.7016, Cohen's d =−0.15)" (p.210). • "The change in energy intake from baseline to six months among subjects in the LI group was significantly greater than among those in the control group. This difference, however, was not sustained at 12 months. In this study, the authors attempted to induce participants to improve their dietary and physical activity habits by supporting them in incorporating into their lifestyles dietary and physical activity behavior for diabetes prevention. However, this result suggests that indirect lifestyle intervention using LISS-DP was effective only during the actual intervention period (six months). In terms of primary prevention, continuous lifestyle support

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
			have caused some sampling bias, such as in terms of higher educational status or greater availability of information seeking. Finally, the results were limited by the self-reporting nature of the questionnaire. Participants answered all the questions based on their subjective perceptions" (p.212).	would be necessary to maintain preventive behavior in a healthy population" (p.211). <u>Changes in fat-energy ratio between baseline and the end of the intervention period (ie. baseline – 6 months, final follow up at 12 mons)</u> • "No difference was found in fat-energy ratio between the LI group and the control group. The changes in the fat-energy ratio in the LI group and the control group were 0.39% and −0.56%, respectively, at three months, $p = 0.2396$, Cohen's $d = -0.14$; 0.76% and −0.82%, respectively, at six months, $p = 0.0644$, Cohen's $d = -0.24$; and 0.44% and −0.25%, respec- tively, at 12 months $p = 0.3564$, Cohen's $d = -0.10$" (p.210). <u>Changes in physical activity levels Between baseline and the end of the intervention period (ie.</u>

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				<u>baseline – 6 months, final follow up at 12 mons)</u> • "No difference was found in physical activity energy expenditure between the LI group and the control group. The changes in physical activity energy expenditure in the LI group and the control group were −5.57 and −19.89 kcal/day, respectively, at three months, p = 0.9796, Cohen's d = 0.02; −15.77 and 28.79 kcal/day, respectively, at six months, p = 0.2947, Cohen's d = −0.07; and −4.73 and −70.34 kcal/day, respectively, at 12 months, p = 0.4302, Cohen's d = 0.11" (p.210). • "Physical activity expenditure was also unchanged during the study period" (p.212). <u>Changes in biomedical data (ie. diff in baseline - final follow up at 12 mons)</u> • "No difference was found in BMI; BMI values in the LI group and the control group were 22.5 and 22.1, respectively p = 0.1521. Waist

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				circumferences in the LI group and the control group were 79.4 and 80.6 cm, respectively, p = 0.8195. The other biomedical data followed a similar pattern. No adverse events were observed in participants" (p.211). <u>Acceptance rate</u> • "The present study achieved a higher acceptance rate (40.1%) than some previous preventive studies for relatives of type 2 diabetes patients [42,43]. Moreover, though healthy individuals some- times have difficulty in being motivated to participate in lifestyle intervention, the dropout rate during the intervention period in this study was less than 20%, which was regarded as good [44]. The tolerable dropout ratio in the present study suggests that lifestyle intervention by means of LISS-DP was not a burden for the subjects and permitted their continued participation" (p.211).

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				• "Unlike in previous research, the participants' BMI at baseline in the present study was at a normal level of 22 kg/m2 ; thus, there was no necessity for the participants in this study to reduce their BMI" (p.212). <u>Conclusions</u>: • "This study suggests that a computer-based, non-face-to-face lifestyle intervention that can easily provide education to incorporate healthy dietary and physical activity behavior into participants' daily lives leads the offspring of type 2 diabetic patients to reduce dietary intake only during the intervention period. However, this intervention was not associated with successful long-term modification of lifestyle, and no changes were found in the fat-energy ratio, physical activity expenditure level, and biomedical data such as BMI. There is a possible

Citation Downs and Black Study Design	Setting	Description of prevention programs/activities	Review authors' assessment of included study quality/review strengths & weaknesses	Main findings
				necessity for the offspring of patients with type 2 diabetes to continuously receive lifestyle interventions, such as with compute based, non-face-to-face lifestyle intervention" (p.213).
	•	•	•	•

Definition of 'At Risk' by Study

Table 17: Definition of 'at risk' by included study

Study	Population	Risk definition or diabetes definition
Aguiar, 2014	Adults ≥ 18 at-risk or prediabetic	risk not defined
Dunkley, 2014	Adults ≥ 18 high risk of developing type 2 diabetes (for example, obese, sedentary lifestyle, family history of diabetes, older age, metabolic syndrome, impaired glucose regulation, prediabetes, or elevated diabetes risk score	elevated BMI; elevated diabetes risk score, American Diabetes Association [ADA] [66]); raised random, fasting, or 2-h glucose (finger prick or venous sample); older age; ethnicity; family history of diabetes; and previous medical history of cardiovascular disease, polycystic ovary syndrome, gestational diabetes mellitus, metabolic syndrome, or elevated BP or lipids
Dunkley, 2012	Adults ≥ 18 with metabolic syndrome.	The NCEP definition [2] of metabolic syndrome was adopted by the majority of studies, one study used the earlier WHO definition [1] and one used the more recently developed IDF criteria [4]
Everson-Hock, 2013	Adults > 18 from a low-SES group, within the UK	Low socioeconomic groups in the UK
Geng, 2013	Adults non-diabetic at baseline	Hypertension primary disease as risk Different criteria per included study (i.e.) different variations e.g. IGF cutoffs, IFG cutoffs, WHO, HbA1c>110% ULN, FPG≥126 mg/dl twice, FPG≥7 mmol/l or OGTT2hr ≥11.1 mmol/l twice, 1985 WHO criteria; FPG>6.7 mmol/L twice, if no, OGTT
Geng, 2012	Adults non-diabetic at baseline having at least one cardiovascular disease or cardiovascular risk	Risk defined as: • non-diabetic patients with hypertension • non-diabetic patients with • heart failure

Study	Population	Risk definition or diabetes definition
		• impaired glucose tolerance (IGT) with cardiovascular disease or risk factors • non-diabetic patients with ischemic stroke • non-diabetic patients with coronary artery, peripheral vascular, cerebrovascular disease or end-stage diabetes New-onset diabetes was defined differently among the trials and most used the 1999 WHO criteria of a fasting plasma glucose of ≥126 mg/dl in patients without diabetes at the time of enrollment
Gillett, 2012	Adults with IGT or IFG (mainly IGT)	Intermediate hyperglycemia
Grant, 2009	Adult with impaired glucose tolerance, only with the exception of one trial (Wang YX 2005) which involved those with impaired fasting tolerance (IFG) in addition to those with IGT.	The diagnostic criteria used in the trials were mainly based on the WHO criteria
Greaves, 2011	"Adults (18 years and over) at risk of developing type 2 diabetes, selected because they were obese, overweight, sedentary, had hypertension, impaired fasting glucose, impaired glucose tolerance, hyperlipidaemia, metabolic syndrome, polycystic ovarian syndrome, gestational diabetes, a family history of type 2 diabetes or cardiovascular disease, or had been identified as having a high cardiovascular disease risk score (e.g. using a validated risk score such as Q-RISK or Framingham)."p2	risk score such as Q-RISK or Framingham

Study	Population	Risk definition or diabetes definition
Hopper, 2011	• Adults with IGT, IFG •"Trials included participants with established cardiovascular disease, one or more cardiac risk factors, risk factors for diabetes, or elevated body mass index as entry criteria"p815	The definition of IGT and IFG contemporaneous with the reported study was taken for inclusion.
Johnson, 2013	adults at risk from Type 2 diabetes, and with raised blood glucose levels	Varied: American Diabetes Association risk score > 10, BMI >24 kg/m2, FPG levels, IGF levels, family history, history of risk factors, FINDRISK score, Diabetes Risk Score
Malkawi, 2012	People who were at higher risk of developing type 2 diabetes in the future.	Not defined
Merlotti, 2014	High risk adult population	Not defined
Phung, 2012	Adults with prediabetes	Prediabetes defined as: IGT, IFG, or A1C between 5.7% and 6.7%
Phung, 2011	Patients at high-risk of developing T2D (ages- 34+) "e.g. impaired glucose tolerance, impaired fasting glucose, HbA1c 39–46 mmol ⁄ mol (5.7–6.4%), history of gestational diabetes or obesity	"Definitions of increased diabetes risk varied among elevated BMI, elevated random blood glucose, impaired fasting glucose and impaired glucose tolerance. Definitions of diabetes development also varied, but most trials used criteria set by the World Health Organization [3,23,25,27,30,31,33,34] or the American Diabetes Association [5,6,26,27,34]."p950
Schellenberg, 2013	Adults > 18 yrs with risk factors suggesting increased risk of T2D	•"Our operational definition for patients at risk for diabetes included the metabolic syndrome, pre-diabetes, insulin resistance, impaired fasting glucose, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and the Reaven syndrome. For simplicity, we refer to these patients as "high-risk patients."p544

Study	Population	Risk definition or diabetes definition
Sherifali, 2013	Asymptomatic adults 18 years or older at average or high risk for T2DM complications	Not defined
Shirani, 2013	Ref 21 includes population with T2D, all other pops are prediabetic	Not defined
Song, 2012	individuals with hypertension or others high risk factors	Risk pop included those with: Essential hypertension Heart failure Impaired glucose tolerance Cardiocerebrovascular diseases
Waugh, 2013	Adults with Intermediate hyperglycemia i.e. undiagnosed T2DM or IGT/IFG.	HbA1c levels of 6.0–6.4% English Vascular Risk manual suggests a cut-off for HbA1c level of < 6% as normal and a level of 6.5% as confirming diabetes if symptoms are present. The intermediate results 'require further investigation'. The International Expert Group regards a HbA1c level of 6.5% as diagnostic. In the USA, a lower threshold of 5.7% is advocated.
Yoon, 2013	High risk sample with impaired glucose tolerance	Impaired glucose tolerance and related conditions
Yuen, 2010	IGT or IFG or both	T2DM via OGTT or FPG based on ADA 1997 criteria or WHO 1985 or WHO 1999 definitions.
Hellgren, 2013	Adults with IGT	Adults with a FINDRISC score of ≥15 (0–26) in the questionnaire were examined with a fasting plasma glucose and an OGTT. The score cutoff was lowered to >11 for the last 4000 questionnaires. Individuals 35–75 years old with IGT were eligible for this study
Lian, 2014	Adults with IGT	IGT with a 2-hour plasma glucose concentration of 7.8–11.1 mmol/L after a 75-g oral glucose tolerance test (OGTT) and fasting plasma glucose greater than 7.0 mmol/L

Study	Population	Risk definition or diabetes definition
		(according to World Health Organization 1999 criteria
Long, 2014	Eligible participants were aged 40 to 69 years, not known to have diabetes, and with a Cambridge Diabetes Risk Score > 0.17, corresponding to the top 25% of participants' risk distribution (18).[i.e. screen detected]	Cambridge Diabetes Risk Score > 0.17, corresponding to the top 25% of participants' risk distribution (18).[i.e. screen detected]
Salas-Salvado, 2014	Adults without diabetes at baseline, without CVD but had at least 3 or more cardiovascular risk factors	Cardiovascular risk factors, namely current smoking, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol levels, overweight or obesity, and family history of premature CVD
Tokunaga-Nakawatase, 2014	Adults 30-60 with first degree diabetic relative	Adults 30-60 with first degree diabetic relative

Recommended Guidelines for T2D Screening in Canada

Table 18: Guidelines for T2D screening in Canada

Organization	Quoted recommendations for screening for T2D in Canada
Canadian Task Force on Preventive Health Care	• "For adults at low to moderate risk of diabetes (determined with a validated risk calculator), we recommend not routinely screening for type 2 diabetes. (Weak recommendation; low-quality evidence) • For adults at high risk of diabetes (determined with a validated risk calculator), we recommend routinely screening every 3–5 years with A1C. (Weak recommendation; low-quality evidence) • For adults at very high risk of diabetes (determined with a validated risk calculator), we recommend routine screening annually with A1C. (Weak recommendation; low-quality evidence)." **Reference:** Jean-Marie Ekoé, M. D., CSPQ, P., FRCPC Thomas Ransom, M. D., FRCPC Ronald Goldenberg, M. D., & Video, S. Screening for Type 1 and Type 2 Diabetes http://canadiantaskforce.ca/ctfphc-guidelines/2012-type-2-diabetes/
Canadian Diabetes Association, Clinical practice guidelines	• "All individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria [Grade D, Consensus]. • Screening for diabetes using FPG and/or A1C should be performed every 3 years in individuals ≥40 years of age or at high risk using a risk calculator [Grade D, Consensus]. More frequent and/or earlier testing with either FPG and/or A1C or 2hPG in a 75 g OGTT should be considered in those at very high risk using a risk calculator or in people with additional risk factors for diabetes [Grade D, Consensus]. • Testing with 2hPG in a 75 g OGTT should be undertaken in individuals with FPG 6.1–6.9 mmol/L and/or A1C 6.0%–6.4% in order to identify individuals with IGT or diabetes [Grade D, Consensus]. • Testing with 2hPG in a 75 g OGTT may be undertaken in individuals with FPG 5.6–6.0 mmol/L and/or A1C 5.5%–5.9% and ≥1 risk factor(s) in order to identify individuals with IGT or diabetes [Grade D, Consensus]." **Reference:** Canadian Task Force on Preventive Health Care. (2012). Recommendations on screening for type 2 diabetes in adults. Canadian Medical Association Journal, 184(15), 1687-1696.http://guidelines.diabetes.ca/browse/chapter4

Comparators used for drug interventions within systematic review literature

Table 19: Drug intervention vs comparators for included systematic reviews

Drug used as an intervention	Systematic Review	Breakdown of the type of comparator used for drug interventions
Angiotensin Converting enzyme inhibitors (ACEIs)	Geng, 2013	Out of 9 primary studies included in the systematic review: • 1/9 = ACEI vs Hydrochlorothiazide (diuretic) • 1/9 = ACEI vs (diuretic or Ca channel blocker) • 1/9 = ACEI vs diuretic or beta blocker • 1/9 = ACEI vs (beta blocker/diuretic or Ca channel blocker) • 5/9= ACEI vs placebo
Angiotensin receptor blockers (ARBs)	Geng 2012	Out of 11 primary studies included in the systematic review: • 6/11 = ARB vs Placebo • 2/11 = ARB vs Non-ARB- • 2/11 = ARB vs Amlodipine (Ca channel blocker) 1/11 = ARB vs Atenolol (beta blocker)
	Song 2012	Out of 11 primary studies included in the systematic review: • 5/11 = ARB vs Placebo • 2/11 = ARB vs Diuretic and/or beta blocker • 2/11 = ARB vs Amlodipine (Ca channel blocker) • 1/11 = ARB vs Nateglinide (oral diabetes drug) 1/11 = ARB vs Non-ARB
Oral anti-diabetic drugs (OAD)	Phung, 2012	Out of 13 primary studies included in the systematic review: • 11/13 = OAD vs placebo • 2/13 = OAD vs control (not specified)
	Phung, 2011	Out of 20 primary studies included in the systematic review: • 16/20 = OAD vs placebo • 3/20 = OAD vs control • 1/20 = OAD vs other OAs

B. Additional Resources for Economic Section of the Report

Full Economic Report

Title: Screening and prevention of type 2 diabetes - Economic Evaluations

Author: Michel Grignon, McMaster University, July 2015

Economic Rationale of T2D Prevention and Screening

Prevention

Since T2D and its complications are costly to treat, an intervention that delays or prevents its onset not only adds to longevity and quality of life, but also saves expenditures to the healthcare system (through averted costs to treatments of diabetes and its complications) in the following ways:

- If the intervention delays but does not prevent diabetes, the health system will save costs at each period but each individual cohort will cost more (cost of T2D plus cost of the intervention).
- If the intervention not only delays but prevents diabetes in a significant number of cases, savings will be larger and each cohort will cost less over their life-time.
- If savings on treatment of T2D or its complications exceed the costs of the intervention, the intervention is said to be cost-saving and there is no reason why it should not be implemented.
- If savings are not great enough to offset the cost of the intervention, the intervention can still generate utility (better or longer life) and will be evaluated through the cost per unit of outcome (utility) generated (see below for more detail) and the intervention is deemed cost-effective if the cost per unit of outcome is below a given threshold.

The outcome could be measured as the number of cases averted, but that would not allow decision-makers to compare the intervention with interventions to treat or prevent other conditions. This is why an outcome that can be compared across interventions for different diseases is preferred. One such outcome is number of years of life gained, but, because T2D affects quality of life as well as longevity, a better outcome measure is the number of quality-adjusted life-years (QALY) gained through the intervention (how many more years of life in better health). Such analyses are called cost-utility-analyses (CUA) and this review focuses on this approach.

Screening

Similarly, because complications of T2D are very expensive, spending to identify undiagnosed diabetics through screening and providing these newly diagnosed cases treatments to stabilize their diabetes, will save costs for the health care system. If enough cases are averted to offset the initial cost of the intervention screening can be said to be cost-saving; otherwise, as in the case of prevention, the intervention can still add utility to patients and a cost per outcome unit (QALYs gained) will be presented to decision-makers as a measure of its cost effectiveness. Screening will be deemed cost-effective if the cost per unit is below a given threshold.

Economic Review Objective

This economic review will assess the methods and present the findings of published cost-utility analyses (CUA) to help understand the cost-effectiveness of two types of possible interventions for T2D:

1. interventions that aim to prevent T2D development among individuals at risk for T2D; or
2. interventions that screen asymptomatic adults, either as a general population group or by targeting specific at-risk subpopulations, in order to detect T2D sooner and prevent or mitigate complications associated with the disease

It must be noted that some of the analyses discussed in this review do not present any QALYs gained because they find that the intervention is cost-saving.

Cost Utility Analysis (CUA) Methods

A CUA is a type of economic analysis that allows us to assess the health benefit of an intervention, i.e., the additional quantity and quality of life an intervention provides versus the cost of the resources it takes to implement it (net of savings to the health care system). The additional cost of the new intervention per unit of health gain is considered. The intervention may be cost-saving (the net cost is negative), in which case it should be implemented with no need to consider the QALYs involved, or cost-effective (the net cost is positive, but the net cost per unit of outcome is below an accepted threshold), or neither.

CUA Parameters, Variables, & Calculations

CUAs tabulate certain variables in order to evaluate and compare the economics of the interventions in question:

1. Cost (C)
   Definition: The cost per individual of the intervention (prevention or screening)

2. Costs Saved (CS)
   Definition: Costs of treatments that would have occurred if the intervention had not taken place, e.g., for preventive lifestyle interventions: the cost of T2D and its complications; for screening: the cost of treating T2D complications.

   Components:
   - **ΔI =** cases of T2D averted
   - **T** = Treatment cost, which can in turn be decomposed into:
     - **t =** Cost per year of treating a diabetic patient or a complication (case of screening)
     - **d =** duration with diabetes (or the complication)

Computation:
The cost saved is the product of the cost of the treatment, T, and the proportion of cases averted ΔI. Where, **T** is the product of **t**, the cost per year of a diabetic patient, and **d**, the duration with diabetes.

Cost Saving = (T)(ΔI), where T=(t)(d)

3. Gain in utility generated by the intervention (Q)

Definition: The total quality of life that is gained through an intervention. The utility generated by better health-related quality and quantity of life is measured as quality-adjusted life years (QALYs) or disability adjusted life years (DALYs). In our analyses we will focus on quality adjusted life years because it is more comparable to outcomes measured in interventions for other diseases. For prevention programs, Q would measure the improvement in the length and quality of life produced by preventing the onset of diabetes and/or its complications. In the case of screening, quality of life would be improved through delay or reduction of T2D related complications.

Components:

- **QALY**= quality adjusted life year is a measure of health as a combination of the length of life and the health-related quality of life (HRQoL).

Computation:
The use of QALYs puts a value on years of life gained by the intervention through health-related quality of life where 1 = perfect health and 0 = death. A year of life gained in mediocre quality of life (with a rate of 0.5) will have the same value as improving quality of life from 0.5 to 1, without extending duration of life. It is based on weights attributed to various health states and reflecting their utility, i.e. the satisfaction they bring. Instruments such as EQ-5D, the Health Utilities Index, Mark 3 and SF-6D are used to calculate QALYs (1).

4. The difference in Net Cost (NC)

Definition: The cost per individual of the intervention minus savings on treatment.
Components:

- **C**= Cost
- **t** = Cost per year of a diabetic patient
- **d** = duration with diabetes
- **T**= Treatment, i.e. [(t)(d)]
- **ΔI**= cases of T2D averted

Computation: The difference in the net cost is equal to the cost minus the savings on treatments

$$\mathbf{N\,C = (C - T)(\Delta I)}$$

If NC<0 = the intervention is cost saving and a good idea to implement

If NC>0 = the intervention is not cost saving and so we should use ICER to find out if the intervention is deemed to be cost-effective, that is, if its incremental cost per QALY is below an accepted threshold (called "Willingness To Pay" or WTP). This threshold will differ from jurisdiction to jurisdiction. For instance the National Institute for Health and Care Excellence (NICE) in the UK uses a threshold in the range of GBP20,000 to 30,000, or CAD40,000 to 60,000 per QALY.

Overall, the threshold of cost effectiveness is somewhat arbitrary. For this reason, we will not categorize interventions as cost-effective or not. Instead we will provide the ICER as calculated, leaving it to decision makers to decide whether or not an intervention is cost-effective.

5. Incremental Cost Efficiency ratio (ICER)

Definition: ICER is used to compare interventions that are not cost-saving (net cost greater than 0). It is the ratio of NC (net cost) to Q (gains in outcome). A lower ICER means the intervention is more cost-effective (it costs less per unit of outcome). ICERs are needed to compare interventions for different diseases.

Components:

- NC = net cost
- Q = gain in the utility generated by the intervention

Computation:

A low ICER means that implementing the intervention will make the health care system more expensive but will improve the quality of life of the population at a cost that may be deemed reasonable (compared to other uses of the same amount of money.) The numerator of the ICER, net cost, is highly system and intervention dependent. If a health care system can treat T2D more efficiently or cheaply than another system, its net cost will be larger, everything else being the same, and so will the ICER of the same intervention for this system. The denominator, on the contrary, is meant to be (almost) universal: there is no strong reason why different populations would value health states differently. However, not all studies use the same instruments to measure the utility associated with health states, and Q might vary accordingly across studies.

ICER = NC/Q which is the cost per unit of utility generated

Relationship of economic parameters to interventions for T2D

We now provide more details on the parameters listed above and how their values are calculated or estimated in the studies we assessed.

Intervention Cost: C

The cost of an intervention is highly dependent on how the intervention is organized.

A) For preventive interventions, cost depends on a number of factors including:
   - Delivery of the intervention: group basis or individual basis
   - Provider: physician, nurse, alternative health professional
   - Intensity of the intervention (how many visits or meetings for instance)
   - Direct costs of the intervention (doctors' fees)
   - Indirect cost of the intervention (time lost by patients, from work for instance, to receive the services)
   - Frequency of the intervention: whether or not the intervention is repeated over time. The usual procedure in the case of T2D is to conduct the intervention once for three years but some variants rerun it for three or six more years.

   Most studies of preventive interventions that we reviewed were based on the same intervention called the Diabetes Prevention Program (DPP). The study of this program was conducted in the US and found a total cost of $4,000 per person over three years, or approximately $1,300 per year (2–5).

   In another intervention, called the Diabetes Prevention Study (DPS) from Finland (6), the cost of this intervention could not be distinguished from the gains on treatment saved. The only statistic provided from the Diabetes Prevention Study is the difference C – T = $236.

   Other studies found a total cost of approximately $4,000 or lower with a couple of exceptions.

   1) Mortaz et al. state that the lifestyle intervention they use (DPP) cost $500 per year on average in Canada. They do not specify the duration of the intervention but, since their simulation extends over 10 years, we can assume that the cost of the DPP has been averaged over these 10 years, yielding a total cost C of $5,000 (7).
   2) Schaufler and Wolff present an average annual cost of the lifestyle change intervention (the UKDPS) of EUR515 in 2006 (or 515*1.5 to convert Euros in CAD, and again inflated 9 years at 2% per year, or CAD925 in 2015). Since the intervention lasted 17 years on average, this annual cost would bring the total cost of the DPS to the impossible value of CAD16,000. This suggests that Schauffer and Wolff do not mean that the cost per year over the entire horizon of the simulation was EUR515 but that was the cost over the full duration of the intervention (8).

      These two exceptions can be considered unreliable outliers in the distribution and overall, it seems reasonable to assume that the costs of the preventive intervention do not vary greatly and come in at approximately $4,000.

B) The costs associated with screening interventions are more varied than those for preventive interventions. There is the cost of the test itself. This could be smaller or larger depending on

whether or not the test is provided in an opportunistic way during a regular physician visit. The main driver of cost in screening interventions is the cost of routine T2D treatment for newly diagnosed cases and this cost must be used in the computation of screening costs as screening does not improve QALYs by itself, but only in combination with treatment to control glycaemia, such as some combination of drug (such as metformin), lifestyle change, or insulin.

*Effect of prevention and screening interventions on incidence of T2D and cases averted, Δ*I

Prevention

The parameter of interest for preventive interventions is the cumulative incidence of T2D at a given horizon, which is the same as prevalence minus deaths. This parameter is appropriate since it is rare for those diagnosed with T2D to revert back to a pre-diabetic state once diagnosed.

It is estimated based on observed differences within trials: short term studies find that lifestyle change interventions such as the DPP reduce the relative risk of developing T2D (among pre-diabetics) by 40%. This does not mean that the intervention prevents 40% of T2D, as it may only delay its occurrence. The difficulty (and most of the debate) is in the estimation (simulation) of the parameter outside of trials (lifetime simulations). Markov chains and Archimedes are the main types of simulation models used in the literature. Each yields quite a different projection of the cases of T2D averted over a lifetime. After reviewing the evidence, it seems that Archimedes is more valid as a projection model. Studies using this approach (5,6,9) find a difference in cumulative incidence between the intervention and control groups of 11 percentage points (72% to 61%) at 30 years. Markov models generate larger differences, closer to 20 percentage points, but seem to be over-estimates. Accordingly, we will consider 11 percentage points a better estimate of the long-term effect of preventive interventions.

Screening

The parameter of interest for screening is the cumulative incidence of complications.
The value of the parameter will increase with targeting: if screening is very wide, it will include individuals who are not and will not be diabetic and will therefore never develop any complications.

For screening interventions, the number of complications averted is simulated based on the following assumptions:

(a) An assumption of the proportion of the population that consists of undiagnosed diabetics. Based on trials of screening interventions, we can estimate this parameter at around 3% of the population aged 25 and older but this varies with the race/ethnicity, age, blood pressure, and BMI of the population in question.
(b) Because no clinical measures would allow one to observe retrospectively the duration from onset to diagnosis at the time of diagnosis, there is no evidence on the time elapsed between onset and diagnosis in the absence of screening interventions. Two studies (10,11) evaluated in

the review by Li et al. (12) make the assumption that average time between onset and diagnosis is 10 years. Because the screening intervention will take place any time during that period, it reduces the delay by half: on average, true positives in the screening interventions will be diagnosed 5 years after onset instead of 10 in the control group (no screening). Kahn et al. used a more refined approach, allowing time between onset and diagnosis to vary with age (at onset) (9). Screening reduced the number of years of un-diagnosed diabetes by approximately 5 years at age 45 (as in previous studies) but 2 years only at age 60 (because time with un-diagnosed diabetes is much shorter at 60 in the control group).

(c) An assumption of the rate of progression of the disease before clinical diagnosis. Hoerger et al. make the explicit assumption that the disease progresses very slowly before diagnosis (11). It is diagnosed precisely because the process changes and accelerates the progression of the disease.

(d) An implicit assumption is made that previously undiagnosed diabetics will benefit from the intervention to stabilize diabetes in the same way as diabetics diagnosed in standard practice (not through a screening intervention) enrolled in trials of the treatment to stabilize T2D. This is a possibly dubious assumption, as one can anticipate that undiagnosed diabetics are also more likely on average to be non-compliant with the treatment once they have been diagnosed through screening.

The average cost of treatment for T2D and its complications over the course of the disease

We restrict costs to direct medical costs, i.e., costs from the perspective of the health care system; some studies present both the health care system and societal perspectives in which case, we report on the health care system perspective only. We also exclude studies using a societal perspective only. The cost of treatment is, of course, highly system dependent and studies use varying values for the cost of treatment even for the same system. We explain below why we believe some values for the cost of treatment are more reliable than others.

Cost of treatment in within-trial studies

The cost of treatment for T2D is straightforward to calculate in within-trial studies. It is simply the difference between the average direct medical cost observed in the control arm and in the intervention arm. Three such studies have been conducted in the US. Two (2,13) of these find the cost per year of a diabetic patient to be approximately $2,200. One other study finds the cost to be $4, 250 (3).

Cost of treatment in out-of-trial simulations

Determining the cost of treatment is complex in out-of-trial simulations where a value cannot be observed and must be estimated instead. For each observation in the cohort or population that is predicted to develop T2D in both arms of the simulation, a cost of T2D and its complications must be imputed, based on estimates drawn from the literature (other studies). Different methods are used to estimate the cost per year of a diabetic patient. The annual cost of a non-observed T2D can be itemized in a number of ways.

a) Bottom-up method: Lists and sums the cost of all services that a patient with T2D should receive. This leads to very large cost estimates.
b) Top-Down: Meaning they are either regression-based or attributable fractions. The regression method consists simply in running a regression of total health care costs of the individuals on a series of variables including a binary variable indicating whether the individual suffers from T2D (or one of its complications). The coefficient for the regression with the disease present measures the cost of the disease, everything else being the same. The attributable fraction assigns a portion of total cost to T2D.
c) In top-down methods, regression analysis is currently the preferred method because it does not require investigator-dependent decisions on what services should be attributed to T2D. The disadvantage of estimating by regression is that it is vulnerable to specification errors, most notably omitted variables. Any omitted variable that correlates with both costs and T2D incidence will wrongly lead the investigator to attribute disease costs to T2D that are not caused by it so that eliminating the disease through the intervention would save only part of the cost of treatment.

Most simulation studies use a value of around $3,000 for the cost per year of diabetic patient in Canada and the US (7), and $2,100 for Australia (5). The only outlier is Anderson but we explain in the synthesis section what we think is a mistake in this author's estimate of the cost per year of a diabetic patient (4).

Time between the onset of T2D and death

The time between the onset of T2D and death is often estimated at around 10 years. A key assumption is that this time does not vary across arms and that the intervention only delays the onset of diabetes but does not affect its course once started. This seems to be confirmed by observational studies within Li et al. which used a 20-year maximum follow up (12). However, it may be the case that beyond 20 years the duration of T2D differs between intervention and control arms.

Utility of preventing diabetes or its complications: Determining Q

Q refers to the potential non-monetary benefit of the intervention. Preventing diabetes or its complications averts loss of health status in terms of the quality and quantity of a person's life and brings individuals to a higher level of utility over their lifetime, i.e., more and better years of life. Most interventions to prevent or delay T2D and its complications do not have much impact on life expectancy[1] but they have an impact on quality of life. We looked to the studies we assessed for the review in order to determine an appropriate value for Q.

[1] This is a bit disappointing from a public health perspective but makes the life of the economist much easier. When an intervention prolongs life, the analyst must simulate the cost of these extra years of life; if they take place after the age of 70 or 80, chances are that some of these extra years will be lived with dementia or other

For within-trial studies, the evaluation is a straightforward comparison of average quality of life in each arm of the trial and this number depends on the instrument (questionnaire) used to assign a utility value to a health state. There are three main generic validated instruments available to economists to calculate the health utility of an intervention. They include: Quality of Life (QoL), Quality of Wellbeing (QWB), Health Utility Index (HUI). The studies in this review mainly used the QWB instrument. Studies found an average gain of 0.15 QALYs over 10 years for Diabetes Prevention Program (DPP)-like interventions. This means that the intervention increased quality of life on average by the equivalent of 1.8 months of life in perfect health.

Other within-trial studies found much lower gains in QALYs (0.003) over shorter periods of observation (the period of observation is only 7 months in Irvine et al. (15) and four years in Sagarra et al. (16)). Out-of-trial projections must proceed differently and assign a quality score to each possible health state in the simulation (similar to what has to be done for the cost of treatment above)[2]. The gain in QALY will not only depend on the instrument used but also on how detailed the description of health states is, for example, how many possible states are simulated. Gillett et al. found the lowest gain in QALY over the lifetime, at 0.08 for a DPS-type intervention (6). On the other hand, Schaufler and Wolff found an incredibly high gain of 2.91 (8). This higher gain reflects the large gains in life expectancy predicted by their model, which makes their study a clear outlier. Projections in Eddy et al. were based on an Archimedes model (5). These authors found that preventive interventions similar to the DPP (if delivered per individual, as opposed to by group) produced a total lifetime gain of 0.16 QALYs. Projections based on Markov chains are more optimistic and found gains between 0.29 (Mortaz et al. (7) for Canada) and 0.39 (Palmer and Tucker (17)). However, Palmer and Tucker, likely include an overly optimistic projection of the proportion of cases of T2D averted. Using their findings on QALY gained per case averted but with a more realistic projection of the number of cases averted would also yield a gain of 0.29 in QALYs, similar to the estimate in Mortaz et al.(7).

Anderson used 0.29 as the baseline value for Q (4). She stated that three studies conducted in Australia as reported by Dalziel and Segal found Q = 0.29 but a direct examination of that review found that it reported a gain not of 0.29 but of 0.41 for an ILC intervention conducted in Australia instead (4).

Careful consideration of the studies mentioned above led us to use Q = 0.16 as our baseline outcome measure for ILC interventions, and 0.29 for sensitivity analyses.

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neuro-degenerative diseases that could not develop if the individual had died earlier. This issue of unrelated costs of prolonging a life (14) is never discussed in the studies reviewed here.

[2] In most instances, the analysts use estimate of the loss in quality of life associated with various complications of the disease and then add them if the individual suffers from several complications at the same time. This additive assumption is of course highly disputable and certainly over-estimates Q, but it is impossible to know by how much.

Variations in values for Q among analyses (simulations) of screening strategies are much wider. Kahn et al. used a gain in QALY of between 0.05 (0.6 months) and 0.19 (2.4 months) per individual screened (hence much more per diabetic) (9) whereas Hoerger et al. used a much smaller gain one tenth as big of only between 0.004 and 0.018 (six days) (11). CDC-Diabetes-Cost-Effectiveness-Study-Group used 0.06 (10), close to Kahn et al., but it is not reliable, as it is derived from DCCT, a trial of a treatment of T1DM, not T2D.

Anderson suggests that another way to measure cost-efficiency is to calculate the number of cases (or complications) that the intervention needs to be able to avert to be cost saving (known as A), so that A = (P)(C), where P is the size of the target population (4). To be cost-effective: A must be greater than (P)(C)/T+[(Q)(W)].

Review of the Economic Evidence

Economic Evidence Described

In this review of the economic evidence we evaluated two types of evidence:

1) Evidence from empirical studies: This evidence considered similar, non-identical interventions aimed at changing lifestyles or detecting diabetics estimated values for the parameters (C, ΔI,T,Q) and calculated the resulting ICER (or the difference between C and (ΔI)(T) if negative).
2) Evidence from simulations: This type of evidence used values for the parameters estimated elsewhere to calculate the cost-effectiveness of these interventions in the long term, outside of the range of observation.

Empirical evidence is more robust but it is usually restricted to a relatively short period of time (the maximum is 10 years); however, we have good reason to believe that the benefits of such interventions will be felt more strongly over longer periods of time. This is especially the case for primary prevention (a one-time intervention followed by several years of benefits). Therefore, we need to rely both on purely empirical (within-trial) as well as simulated (outside-of-trial) studies that use costs projected over the lifetime.

Study Interpretation

Below you will find a narrative description of the economic studies and their findings. We did not calculate an average ICER in an approach similar to meta-analysis because ICERs are so intervention, system, and study dependent. Also, studies varied along a number of dimensions including:

- intervention[3] type,
- comparator -placebo, standard, drug alone -,

[3] Saha et al. identified 12 intensive lifestyle interventions, 6 interventions to increase physical activity, 5 to change diets, 14 combinations of dietary and physical, and 9 including a drug plus any of the above (18).

- target groups – by age and risk factors-,
- settings- national or local-, country,
- time discount rates – some studies use different total dependency ratio (TDR) for costs and benefits -time horizons,
- various outcome measures for quality of life and methods were used e.g., decision trees, Markov models, life-tables or Archimedes models

As a part of our narrative assessment we always present findings in the context of the measures that studies used to interpret economic findings. We consider which assumptions were made to derive values for C, T, and ΔI, and what instrument was used to attribute utility values (Q) to various health states. Most studies identified used the self-administered questionnaire on well-being (QWB-SA) but two used a different instrument, the EuroQoL.

Only a limited number of studies were found that met our inclusion criteria. In order to maximize the quantity of information available, we included all studies even those with methodological flaws. Most of these flaws could be fixed easily and we present the findings of the studies after correcting for these mistakes. It is not orthodox practice to do this in clinical studies but we present arguments to convince the reader of the validity of our corrections. The only exception relates to studies based on self-reports of health care services utilization (rather than direct observation of costs or imputation of average costs). If a study was based on self-reports, we included its findings but do not give much credit to its conclusions. We also make clear in the description below what our preferred model is for the case of the US and what conclusions we can draw from it in terms of ICER.

Economics Specific Inclusion Criteria

All studies producing an ICER or a value for net costs were included either directly, if they were published after 2009 or indirectly, as listed in one of two systematic reviews published in 2010. We focused our attention on studies that calculated the cost of the ICER of interventions ICER from the perspective of the healthcare system rather than those using a broader societal perspective. This means that direct medical costs such as clinical services, hospitalization, and medications are considered in the assessment and interpretation of the results while indirect costs of both the intervention and treatment are not included. The indirect cost of the intervention is the cost in time and travel incurred by patients to receive the intervention and the indirect cost of treatments averted is the cost in time and travel incurred by patients to receive the treatment.

Narrative Description of Economic Studies

Nature of the Economic Literature

The economic review evidence for preventive interventions of T2D and screening for T2D was limited. Ultimately only two reviews made it into the discussion below. Both insisted on the variability of findings within the studies included (12,18). They agreed that similar interventions can be found to be either

cost-saving by some studies or to have an ICER well above $150,000 per QALY according to other studies. One review identified 12 intensive lifestyle interventions, 6 interventions to increase physical activity, 5 interventions to change diets, 14 interventions combining diet and physical activity and 9 interventions including drugs plus any of the preceding combinations (18). The other reviewed all types of preventive interventions as well as screening and was organized around interventions rather than studies (12). We used the findings from these two reviews, revisit some of the most critical individual studies cited, and add a description of twelve studies published since 2010.

Interventions to prevent T2D among pre-diabetics

Overall we found that reviews of empirical studies converged in their conclusions. Preventive interventions were never cost-saving in the short-to-mid run (10 years and less) but most were in the low range of ICER, between $4,000 and $30,000 (in 2015 US$). No short-run (within trial) studies were identified in Saha et al. (18) or Li et al. (18).

Five[4] economic studies published since the reviews conducted in 2010 were also identified. One concluded that the intervention is cost-saving (13), but it was based on self- reported adverse events (hospitalizations) and as a result is considered the least reliable. The other four (two from the US, one from Britain and one from Spain) used actual treatment cost in both intervention and control arms (2,3,15,16).The ICER values of these economic studies ranged between $4000 and $30 000. The variation of values reflects individual differences between studies such as intervention components, intervention cost, follow-up period and participant characteristics. Overall, ambitious follow ups conducted in the US revealed that T2D prevention costs between $10,000 and $20,000 per QALY (2,3). The cost per QALY will likely be greater in a Canadian context where T is lower. Individual study results can be seen in the table 1 below.

***Table* 1:** *Cost range of individual study findings for preventive interventions (cost saving to cost-effective)*

Author	Finding	Interpretation
Lawlor et al. (13)	• Cost saving	The results of this study were based on self-reported adverse events and are therefore considered less reliable.

[4] An additional study, Lohse et al., finds ILC interventions to be cost-saving when applied to the very specific population of pregnant women with Gestational Diabetes Mellitus, in sites in India and Israel. They use a high value of $88,000 for the lifetime cost of treatment of T2D (drawn from the CORE model) that they then adjust to the cost of health care in both countries, at $1,300 in India and $26,700 in Israel. The value for C is also very low, at between $10 and $50 in India and at $100 in Israel. Costs are discounted at 3% per year (19).

Sagarra et al. (16)	• This Spanish study found an ICER of $4,000.	The ICER value reflects the low cost of the intervention which was $125 per patient.
Diabetes-Prevention-Program-Research-Group (2)	• This US study found an ICER of $11,000	This US study evaluated an intervention called the Diabetes Prevention Program (DPP). It is a three year intervention[5], costing $4,000 per patient and they observe the subjects over a 10-year period (3 years intervention, 1 year bridge period, and six years follow-up).
Herman et al. (3)	• This US study also based on the Diabetes Prevention Program found an ICER of $20,000.	
Irvine et al. (3)	• Found an ICER of $30,000	This result is restricted to the intervention (no follow up, total period of seven months).

Through the course of reviewing this economic literature, we uncovered an issue related to the models used to simulate cost. We would expect that in the longer run (20 years to lifetime), interventions are at least as effective as they are in the short run[6] and could even become cost-saving. The review by Saha et al. disagrees with this premise (18). It highlights a controversy among epidemiologists as to which model should be used to simulate cases of T2D averted. A Markov chain model can be used to simulate ΔI outside of the follow- up range. Alternatively, a more complex model, called Archimedes can be used (5). The three studies identified in Saha et al. used a Markov model and found a lifetime ICER between $1,000 and $10,000 (18). The study using the Archimedes model found a much higher ICER > $100,000 (5).

[5] The DPP includes 16 weekly education sessions on an individual basis, covering diet and exercise, followed by monthly sessions, individual or group based. The goal is to lose 7% weight. Li et al. calculated average ICERs across studies analyzing the same study and found that on average, screening of un-diagnosed diabetic patients (with treatment to prevent complications) and prevention of diabetes among pre-diabetics were not cost-saving but was in the very low range of ICERs (below $25,000 per QALY) (12).

[6] Unless incidence increases so much in the intervention arm that it becomes substantially higher than in the control beyond the trial and follow-up period, which is unlikely.

Our assessment sheds light on this very confusing debate. Even though the Archimedes model is preferable from an epidemiological perspective and produces much more conservative estimates of ΔI than Markov chain models, the only study (5) using it for cost-effectiveness used an incredibly high value for the cost of the intervention. This study falsely concluded that preventive interventions were not cost- effective in the long run. We recalculated their analysis using a more reasonable value for cost (approximately $4,000 per patient as in the DPP). Our results showed intervention costs between $5,000 and $27,000 per QALY gained.

Since Saha et al. (18) and Li et al. (12) were published, 8 other English-language primary studies were conducted. These studies contain simulations of lifetime costs and benefits of the prevention of diabetes, yielding 10 ICERs (4,6–8,17,20–22). These studies showed a range of effectiveness from cost-saving to an ICER of $30 000 per QALY (depending on the age the intervention was applied). However; one of these studies used a societal perspective[7] rather than a healthcare system perspective (22) and another was based on self-reported survey data, which makes their results less reliable (21).

Neumann et al. found that the intervention was cost-saving if applied to 30-to-50 year olds in Germany and would cost $30,000 per QALY if applied to patients aged 75 or older. However, these authors (22) used a societal perspective which is not fully comparable to CUA done from the perspective of the health care system[8]. It is important to note that ICERs are not always lower for cost estimates from the societal perspective compared to the healthcare system perspective. Some studies find societal ICERs greater than those calculated from the perspective of the health care system. Castro-Rios et al. also finds the intervention to be cost-saving in the long run in Mexico but it is based on self-reported survey data, which makes their results less reliable (21).

Most other studies were too heterogeneous to compare directly as a result of differences among individual studies or discrepancies in the values used to calculate cost. Despite these differences, studies followed the same pattern and converged toward a low cost per QALY, between 0 and $10,000 (4,6–8,17,20). Specific details for these individual studies can be seen in the table below.

[7] It is important to note that ICERs are not always lower for cost estimates from the societal perspective compared to the healthcare system perspective. Some studies find societal ICERs greater than those calculated from the perspective of the health care system.

[8] This includes somewhat difficult to justify estimates for indirect costs of the intervention and the disease.

Table 2: *Simulation study findings for preventive interventions (heterogeneous)*

Author	Findings	Interpretation
Anderson (4)	• standard DPP implemented over three years is cost-saving in the long-run • simulates variants of the DPP sustained over six or ten years but these are never seriously considered in the real world and are not discussed here) but she uses an extremely high value for T, at $5,600 per year, whereas most other estimates are around $3,000 per year	Used the total cost of diabetes but does not subtract the cost of a pre-diabetic. The intervention will not bring the patient back to NGT but will make sure they remain at the IGT stage and do not become diabetic, therefore, the right value for t should be the difference between the cost of a patient with T2D and that of a patient with IGT. If I use a more sensible value for T (at $3,000 per year), her simulation predicts an ICER of $4,000.
Gillett et al. (6)	• Found ICER of $3,000 in the UK	
Schaufler & Wolff (8)	• Estimated ICER at $1,000 in Germany	
Palmer & Tucker (17)	• Found $7,000 per QALY in Australia	The published result is that the intervention is cost-saving, but it uses a much too generous value for I, generated by a Markov simulation. Using instead a more conservative one, used in the sensitivity analysis of their study, and much closer to what Archimedes or an observational study conducted in China, Li et al. [2010] find, the intervention ceases to cost-saving and becomes (very) cost-effective at $7,000 per QALY.
Bertram et al. (20)	• ICER of $17,000 but it is per DALY	This result was based on DALY rather than QALY, hence it is not fully comparable.
Mortaz et al. (7)	• Found an intervention to screen at risk individuals every	It is impossible to compare it to other preventive interventions because it does

	3 years and preventing or treating diabetes in Canada to be cost-saving.	not separate the ICER of the preventive interventions (preventing per-diabetes to become diabetes) and the ICER of the secondary prevention intervention (preventing complications of diabetes among the newly diagnosed diabetics).

We conclude that interventions to prevent T2D among pre-diabetics are not cost-saving but their ICERs are in the low to medium range (USD10,000 to 20,000). ICER values are sensitive to national values of C and T as well as targeting. These values are also affected by adherence to the intervention and whether or not non- adherers are allowed to switch to therapeutic treatments (metformin). Therapeutic treatments are less effective than lifestyle changes for adherers but more so for non- adherers. Non-adherers are those who cannot lose weight or cannot lose enough weight. On average, non-adherers only lose 1% weight versus 7% for adherers.

Interventions to detect undiagnosed diabetics and control their T2D to delay or prevent complications:

The case for untargeted screening of undiagnosed diabetics in the general population (starting at a given age) and then treating them to prevent complications of diabetes is fragile. There are very few studies[9] to draw upon and those available tend to contradict one another for reasons probably having to do with their assumptions on ΔI and Q.

[9] A study not selected here even though it is about cost-effectiveness is Waugh et al.: they state that screening interventions are not clinically effective (they do not change clinical results at all) and, as a result, no ICER can be calculated. This is not entirely true, though: they actually write that screening has no effect on mortality at 10 years in a clinical trial with follow up and has some effect with borderline significance on the incidence of cardio-vascular diseases at 5 years, based on another trial. However, simulations of ICER of screening are based on effects of early diagnosis on retinopathy and nephropathy, for which there are no trials but simulations of the effect of treatment that find strong positive effects. Last, Waugh et al. also describe a clinical trial conducted in Denmark, the UK, and the Netherlands (ADDITION) that finds no significant effect on mortality and CVD of intervention versus standard treatment after diagnosis. However, this is not relevant to our topic as we are interested in comparing standard treatment to no treatment at all (23).

Li et al. was the only review that evaluated screening (12). It compared different screening strategies and populations with one another and with no screening. Their findings were based on two primary studies[10] only (10,11). There were three relevant findings from this review:

1) First the authors reported that, one-time, opportunistic, targeted screening of hypertensive patients 45 years or older not diagnosed with diabetes and followed by state-of-the-art treatment to prevent onset of diabetes and complications was not cost-saving but was in the low range of ICERs (below $25,000 per QALY) compared with no screening.
2) Secondly, Li et al. reported strong evidence that non-targeted "one-time universal opportunistic screening for undiagnosed type 2 diabetes among those aged 45 years and older compared with no screening"(p.1885) was not cost-effective (defined as > $100 000 per QALY or life year gained LGY). This finding is attributed to small gains in quality and quantity of life. There were no gains at all for all nondiabetics and relatively small gains even for newly diagnosed diabetics.
3) And finally, the review found strong evidence that universal population[11] screening for those 45 years and older compared with targeted screening in persons with hypertension would not be at all cost-effective (defined as >$100 000 per QALY or life years gained [LGY]).

Since the review by Li et al. was published, two simulation studies calculating ICERs of screening interventions have been conducted and published, all in the US context (9,24). Other published studies, such as Khunti et al. (25), produce cost per case detected, and answer the question: how much does it cost to find one un-diagnosed diabetic? But these studies do not estimate the costs of treating those newly diagnosed diabetics or the gains produced by preventing/delaying complications of diabetes.

Chatterjee et al., is a simulation over three years based on the costs of complications of diabetes derived from Kaiser Permanente, a large medical group in the US. This study involved three simulations of opportunistic screening compared with no screening; of universal screening for diabetes or high-risk prediabetes, and of screening those with risk factors based on age, BMI, blood pressure, waist circumference, lipids, or family history of diabetes. However, it should be noted that 58% of the study

[10] 1) The CDC study found that ICER was increasing with age and recommended targeting the young, but this finding was based on the state of treatments available for cardiovascular diseases at the time they ran their study. With better treatments for these diseases, costs saved on older patients (who are more likely to develop CVD when diabetic) reduce ICER of interventions to screen and diagnose diabetes early (10). 2) Hoerger et al. show ICERs between USD30,000 and USD35,000 (CAD46,000 to CAD53,000 in 2014 dollars) for targeted screening of individuals 55 and older with hypertension. Hoerger et al. also calculated an overall ICER of USD126,000 in 2004 (which would be approximately CAD192,000 in 2015) for universal screening versus targeted screening (11).

[11] The age of population screening for adults in this case was not well defined. One of the studies cited age as $\geq$ 25 and another cited US population. Li et al. 2010 conclude that they are unable to determine how the age of screening affects cost-effectiveness based on discrepancies in the studies their analyses were based on.

population was African American so that the results of this study cannot necessarily be generalized to all populations. Chatterjee et al. found that, for the third type of screening, the savings on complications offset the initial cost of the opportunistic screening intervention for those at higher risk which included those with BMI >35kg/m^2, systolic blood pressure $\geq$ 130mmHg, or age >55 years. All net costs are negative and, in some sub-groups, significantly different from 0 at the usual 5% threshold, but they are always very close to 0. Overall, costs savings are in the order of USD100 per person and per year, and net costs savings are close to USD10 per person and per year. The highest absolute net cost-saving was obtained among patients with a BMI greater than 35, with USD15 per person per year. A safer way to describe such a study would be to state that opportunistic screening targeted at higher- risk adults for diabetes may be cost neutral over three years to the health care system, and yield benefits in quality of life to patients but these benefits are not calculated or presented in the study (24).

Kahn et al. is a simulation using the course of a lifetime as its follow-up time frame. An important assumption is that those diagnosed with T2D through screening would then receive state of the art treatment to control their T2D and delay complications. These clinical parameters might differ from those observed in actual trials of screening because, in a trial, the compliance of individuals with treatment once diagnosed might vary whereas the simulation assumes they all comply fully. Readers should bear these assumptions in mind when considering evidence based on simulations. Kahn et al. found that most screening strategies would yield ICERs in the low range, below USD30,000. These authors used the Archimedes model to project the course of the disease in the intervention and control groups and found the following, in ascending order of ICER:

1. Targeting hypertension (> 140=90mmHg:), every year or every 5 years (2 strategies) costs below $10,000.
2. All 45-75 years-old, every 3 or 5 years or All 35-75 years-old every 3 years (3 strategies), costs around $10,000.
3. All 45-75 years-old every year, all 60-75 years-old every 3 years, or all 30-75 years-old every 6 months, costs more than $15,000 (up to $30,000 per QALY) (9).

The same authors also recommended targeted screening for individuals with hypertension between the ages of 35 and 75. However, there are a few caveats associated with these findings:

1. Differences across strategies are not statistically significant in a cohort of 325 000, because differences in outcome (Q) are small over the population as a whole.
2. The reason why their model found a lower ICER than previous models is that they used a better treatment strategy once diagnosed that used more recent guidelines. They also allowed for repeated sequential screening as opposed to one-time screening.
3. It is really not clear why Kahn et al. (9) assume a gain in QALY from the combination of screening and intervention ten times larger than that assumed by Hoerger et al. (11).

4. Their findings are sensitive to assumptions on Q gains. Decreasing the effect by 50% on quality of life of being diagnosed because of symptoms of diabetes increases the ICER by 30 to 60%.

These two recent simulation studies (9,24) seem to agree that the benefit of early detection per case detected decreases when age increases, simply because detecting T2D at age 35 gives more time to the individual to benefit from delaying complications than if it is detected at age 65. On the other hand, the rate of detection varies with age, first increasing to a peak at age 55 when the prevalence of T2D is high and many are not detected. It then decreases below its initial level. For older individuals, prevalence is high but chances are that they already have been detected.

Overall, the case for screening is not entirely clear even though the estimated ICER is lower in more recent studies at about out $10,000 in the best case scenario, i.e. screening patients with hypertension. More robust evidence is needed on this particular topic.

Conclusions

Our conclusions are based on the following assumptions:

- Cumulative incidence decreases by 11 percentage points due to the preventive intervention;
- The cost of the intervention is $4000;
- On average each patient with T2D spends 10 years with the illness.
- The intervention will be cost-saving as long as t is greater than t_{min}= [4000/(0.11)(9.9)] (1+ 0.03)^{10}.
- If the annual relative cost of treatment for T2D (relative to pre-diabetic patients) is lower than $4,900 (which is very likely in Canada), the intervention is not cost-saving.

Our conclusions are presented as a function of the cost of T2D relative to pre-diabetes because a) the conclusions of studies are mostly sensitive to the cost of T2D relative to pre-diabetes and b) the cost of T2D is system-dependent.

Cost of preventive interventions for T2D:
Most preventive interventions are within the cost-effective range of less than $20,000 per QALY. The ICER is given by the following formula: ICER = C/Q – [(d)(ΔI)/(1+p)^{10} (t/Q), which yields values from $5000 to $15000 for the ICER when t decreases from $4000 to $2000. With a more optimistic estimate of Q at 0.29, ICERs vary between $3000 and $8000 for the same values of t. Overall, then, it seems safe to conclude that interventions to prevent pre-diabetic patients to develop T2D cost between $3000 and $15000 per Quality-adjusted life year gained.

Cost of screening interventions for T2D:
Overall, more robust evidence is needed to evaluate the cost of screening interventions for T2D. In the limited studies available, there was some evidence to suggest that targeted opportunistic screening of at-risk individuals to detect and manage diabetes among high-risk patients (obese and/or with high

blood pressure) may be either cost-saving or cost less than $6,000 per quality-adjusted life year gained. However, it should be noted that there was disagreement between studies on the range of cost[12]. Universal population screening of all adults 45 years-old and older compared with no screening was not at all cost-effective, with a predicted ICER of close to CAD200,000.

References

1. McCabe C. What is cost–utility analysis? [Internet]. 2009 Feb p. 1–6. Report No.: NPR09/1099. Available from: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_cost-util.pdf

2. Diabetes Prevention Program Research Group. The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention An intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012 Apr 1;35(4):723–30.

3. Herman WH, Edelstein SL, Ratner RE, Montez MG, Ackermann RT, Orchard TJ, et al. Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care. 2013;19(3):194–202.

4. Anderson J. Achievable cost saving and cost-effective thresholds for diabetes prevention lifestyle interventions in people aged 65 years and older: a single-payer perspective (Provisional abstract). J Acad Nutr Diet. 2012;112(11):1747–54.

5. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005 Aug 16;143(4):251–64.

6. Gillett M, Royle P, Snaith A, Scotland G, Poobalan A, Imamura M, et al. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technol Assess Winch Engl. 2012 Aug;16(33):1–236, iii – iv.

7. Mortaz S, Duncan, Gray, Badawi A, Wessman C. Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: a Markov model simulation. Clin Outcomes Res. 2012 Apr;91.

8. Schaufler TM, Wolff M. Cost Effectiveness of Preventive Screening Programmes for Type 2 Diabetes Mellitus in Germany. Appl Health Econ Health Policy. 2010;8(3):191–202.

[12] e.g., Hoerger et al. still find ICERs higher than USD30,000 in 2004 for patients with hypertension and over 55 years of age (11).

9. Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. The Lancet. 2010 Apr 23;375(9723):1365–74.

10. The cost-effectiveness of screening for type 2 diabetes. CDC Diabetes Cost-Effectiveness Study Group, Centers for Disease Control and Prevention. JAMA. 1998 Nov 25;280(20):1757–63.

11. Hoerger TJ, Harris R, Hicks KA, Donahue K, Sorensen S, Engelgau M. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. Ann Intern Med. 2004 May 4;140(9):689–99.

12. Li R., Zhang P., Barker L.E., Chowdhury F.M., Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review. Diabetes Care. 2010;33(8):1872–94.

13. Lawlor MS, Blackwell CS, Isom SP, Katula JA, Vitolins MZ, Morgan TM, et al. Cost of a group translation of the Diabetes Prevention Program: Healthy Living Partnerships to Prevent Diabetes. Am J Prev Med. 2013 Apr;44(4 Suppl 4):S381–9.

14.Rappange DR, van Baal PHM, van Exel NJA, Feenstra TL, Rutten FFH, Brouwer WBF. Unrelated medical costs in life-years gained: should they be included in economic evaluations of healthcare interventions? PharmacoEconomics. 2008;26(10):815–30.

15. Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T, et al. Cost-effectiveness of a lifestyle intervention in preventing Type 2 diabetes. Int J Technol Assess Health Care. 2011 Oct;27(4):275–82.

16. Sagarra R, Costa B, Cabré JJ, Solà-Morales O, Barrio F. Lifestyle interventions for diabetes mellitus type 2 prevention. Rev Clínica Esp Engl Ed. 2014 Mar;214(2):59–68.

17. Palmer A, Tucker D. Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis (Provisional abstract). Prim Care Diabetes. 2012;6(2):109–21.

18. Saha S, Gerdtham U-G, Johansson P. Economic Evaluation of Lifestyle Interventions for Preventing Diabetes and Cardiovascular Diseases. Int J Environ Res Public Health. 2010 Aug 9;7(8):3150–95.

19. Lohse N, Marseille E, Kahn JG. Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2011 Nov;115 Suppl 1:S20–5.

20. Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabetologia. 2010 May 1;53(5):875–81.

21. Castro-Rios A, Doubova S, Martinez-Valverde S, Coria-Soto I, Perez-Cuevas R. Potential savings in Mexico from screening and prevention for early diabetes and hypertension (Provisional abstract). Health Aff (Millwood). 2010;29(12):2171–9.

22. Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programmes to prevent diabetes based on an example from Germany: Markov modelling (Structured abstract). Cost Eff Resour Alloc [Internet]. 2011;9(17). Available from: http://www.resource-allocation.com/content/9/1/17/abstract

23. Waugh NR, Shyangdan D, Taylor-Phillips S, Suri G, Hall B. Screening for type 2 diabetes: a short report for the National Screening Committee. Health Technol Assess Winch Engl. 2013 Aug;17(35):1–90.

24. Chatterjee R, Narayan KMV, Lipscomb J, Jackson SL, Long Q, Zhu M, et al. Screening for Diabetes and Prediabetes Should Be Cost-Saving in Patients at High Risk. Diabetes Care. 2013 Jul 1;36(7):1981–7.

25. Khunti K, Gillies CL, Taub NA, Mostafa SA, Hiles SL, Abrams KR, et al. A comparison of cost per case detected of screening strategies for Type 2 diabetes and impaired glucose regulation: Modelling study. Diabetes Res Clin Pract. 2012 Sep;97(3):505–13.

Overview of Economic Literature

Articles were screened based on the inclusion criteria for the project with the additional requirement that the articles contain an economic component. Our Health Economist approved the final list and also added a selection from the Higher School of Economics database.

Economic Citations and Economic Literature Extraction Categorized by Intervention

Economic references considered for inclusion in the economic section of the report are listed by intervention. The citation, study type and notes made about each study's main findings and assumptions are also recorded.

Lifestyle Interventions (i.e. Diet, Exercise, Drug alone or in combination)

1. **Anderson, J. (2012)**. Achievable cost saving and cost-effective thresholds for diabetes prevention lifestyle interventions in people aged 65 years and older: a single-payer perspective (Provisional abstract). *Journal of the Academy of Nutrition and Dietetics*, *112*(11), 1747–1754.

Study type	Cost saving analysis
Notes	This is a very good study, providing estimates of the number of cases to be prevented by a Lifestyle intervention for it to be cost saving or cost-effective. Horizon is 10 years and it is limited to seniors (65 years old and older).
	The main parameters are: • C, cost of the intervention (education program delivered to all pre-diabetics, to a cost of $1,875 per person in the first year, $910 in year 2 and $940 thereafter. • T, cost of treating a diabetic patient (cost per year and number of years of treatment, or time between diagnosis and death). Archimedes provides the base case for both sub-parameters, and a total cost of treatment of $56,371 (lifetime). The other cases are based on a regression model, which likely overestimates cost per year (I guess because of omitted variables) and an attributable fractions model, which likely underestimates it (not sure why). Range for cost of treatment per year is $3,400 to $9,700, with Archimedes at $5,694. Archimedes uses 9.9 years between diagnosis and death. This is the direct cost incurring to Medicare (US) only. • Q, QALYs gained if the patient does not go from pre-diabetic to diabetic. Archimedes finds 0.29, some studies find 0.16, others 0.41) • W, WTP per QALY. She uses very high values, at around $200,000. I re-run her simulations with a more conventional threshold at $50,000.
	She calculates A = C/(T+Q.W), the number of cases the intervention should prevent to be cost-effective or cost-saving, and she compares it to what various studies have found. She uses scenarios from least to most conservative and apply them to three types of interventions (3 year, 6 year and 10 year), but we need to un-bundle her scenarios, so as to use a $50,000 WTP threshold with base-case values for T and Q. When I do this, I find the

	intervention to be almost always CE. I also calculate ICER and find them to be below the $50,000 threshold (and often below 0) in most instances. The only non CE cases are for the 6 and 10 year interventions, non adjusting the cost of the intervention to account for the fact that some pre-diabetics become diabetics and do not receive the intervention as a result (it does not seem realistic not to adjust).
	If I use the base-case value for Q but most conservative value for T (at $20,442 lifetime cost), I find the program to be CE if delivered over 3 years, CE only if we believe Markov simulations of reduced incidence (effect of the intervention) if the program is delivered over 6 years, and never CE (ICER between $102,000 and $148,000) if delivered over 10 years. The main difference between a US-based estimate and an NFL-based one will certainly be in T, the cost of treatment per year. Find data on cost of treatment (direct medical) for diabetes in Canada.

2. **Diabetes Prevention Program Research Group. (2012)**. The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention An intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care*, *35*(4), 723–730. doi:10.2337/dc11-1468

   (See Erratum related to 2012 study: **Diabetes Prevention Group. (2013)**. The 10 year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012; 35:723–730. *Diabetes Care*, *36*(12), 4172–4175. doi:10.2337/dc13-er12c)

Study type	Cost effectiveness: Lifestyle vs Drug (Metformin
Notes	This is based on observed, rather than simulated, data. The intervention (DPP) is a 3 year LS (educational) intervention and they added 7 years follow up with light intervention. The intervention costs approximately $3,000 over the course of the first 3 years, but almost nothing after, yielding a cost of $300 per year on average. There are 3 groups, LS, metformin, and placebo. Gains are low (Q is in the conservative range of Anderson, at 0.15 for LS versus Placebo) as are savings on direct medical costs (approximately $200 per year). Cumulative (10 years) net cost (C - T) is at $1,623 for LS versus placebo, or a cost of $11,000 per QALY gained. Metformin is C-S relative to placebo and the cost per QALY gained in LS versus Metformin is about $12,000. Overall, it is CE because the cost is very low, but it has some effect.

3. **Gagnon, C., Brown, C., Couture, C., Kamga-Ngande, C. N., Hivert, M. F., Baillargeon, J. P., … Langlois, M. F. (2011).** A cost-effective moderate-intensity interdisciplinary weight-management programme for individuals with prediabetes. *Diabetes & Metabolism*, *37*(5), 410–418. doi:10.1016/j.diabet.2011.01.003

Study type	Randomized Control Trial: Counselling/Weight Loss

Notes	Outcome = weight loss. Inter-disciplinary individual intervention compared to group intervention. The latter is cheaper but has no effect on weight loss or metabolism. Impossible to translate in cost per QALY or anything comparable.

4. **Gillett, M., Royle, P., Snaith, A., Scotland, G., Poobalan, A., Imamura, M., Waugh, N. (2012).** Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, *16*(33), 1–236, iii–iv. doi:10.3310/hta16330

Study type	Health Technology Assessment: Diet and Physical Activity
Notes	This is a report to the NHS, detailing methods. To be read carefully.
	Chapter 1 is on the epidemiology of T2DM (90% of cases of diabetes are T2). T2DM is linked to deficiencies in the way glucose is managed in the blood. In normal individuals, two hormones, secreted by the pancreas, are responsible for maintaining glucose levels within a given range (max of 5.5 mmol/l): glucagon increases the level in case of depletion (mostly due to physical activity) and insulin decreases it in case of excess (after nutrition). Insulin is called that because it is generated in a portion of the pancreas called the islets/islands of Langerhans. This chapter also reviews risk factors (age, sex, BMI, ethnicity and family risk) and how T2DM can be screened (pre-diabetes): "It is likely that the diabetes is preceded by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), and that family history could provide opportunities for targeted screening." IGT: fasting glucose is not too high (less than 7 mmol/l) but there is post-prandial hyperglycemia (2 hour level of 7.8 to 11.0 according to WHO). IFG: fasting glucose is too high (greater than 5.5 following ADA and than 6.1 according to WHO, and lower than 6.9, otherwise it is T2DM), but post-prandial levels do not reach those observed in IGT (2 hour level lower than 7.8). Fasting glucose level is measured through an OGTT, oral glucose tolerance test, yielding a measure of FPG, fasting plasma glucose, level.
	Important note: the 5.6-6.1 mmol/l range for FPG makes a huge difference in terms of prevalence (based on a French study named DESIR, IFG prevalence goes from 13% to 40% among men depending on the threshold used (4% to 16% for women) but the risk of progression to T2DM changes dramatically at 6.1 for FPG. Therefore, ADA seems to be too alarming and would not target their screening enough.
	IFG is a much stronger predictor of T2DM than IGT. Most individuals with IGT go back to NGT in 10 years.
	Description of Archimedes from Eddy et al. (2005): treatment costs (T, what could be saved) are estimated based on micro-costing of each episode of care. Cumulative incidence at 30 years is estimated to go from 72% for the at risk population in the baseline scenario to 61% with the DPP intensive LS intervention, at a cost of more than $100,000 per QALY. However, the intervention is CE ($24,000) when applied to those with T2DM (as treatment, rather secondary prevention, rather than primary prevention). Archimedes might be more pessimistic than Markov because of several differences:

	• estimated costs of the DPP, but they are simply drawn from the trial, therefore cannot be the source of the discrepancy, • estimated costs of treatment for complications of T2DM; Anderson uses T estimates generated by Archimedes as her base-case value. However, if other economic analyses use a higher value for T (regression-based), they might find higher cost-savings in favour of the LS intervention • estimated gains in QALYs: on page 77, it is stated that this can be a major source of discrepancy, at least for short term (3 years) in-trial calculations. The trial measures HR-QoL within each arm of the trial and finds a 0.07 difference, but some of it can come from the intervention itself (losing weight is good per se) rather than reduction in T2DM incidence; Archimedes, on the other hand, infers changes in HR-QoL from changes in T2DM prevalence and finds almost no effect (at 3 years). Because QALY gains are very small, ICER is super high. • estimated decline in cumulative incidence at 30 years. • Predicted incidence of complications (retinopathy blindness, gangrene, AMI, stroke) outside of the trial (at 30 years): Archimedes predicts a much lower cumulative incidence rate at 30 years than Markov models, even though survival times are the same. It may be the result of a linear assumption in Archimedes (for the pace of progression to these complications) whereas Markov models follow a different pace assumption where complications arise much faster after a given period of time with T2DM.
	Review of economic studies: • Mention Gillies (2008): 4 strategies (nothing, screening for T2DM only, screening for T2DM and IGT plus LS intervention, and screening for T2DM and IGT plus pharmaceutical intervention). Finds that strategy 3 is more CE than 2 (screening only). • The economic model presented here is from the perspective of the NHS (single payer health care system), over a 20 year horizon and developed on the basis of a SR of clinical trials and a Markov simulation. • Their own modeling allows non adherers (not enough weight loss: 1.1 kg after 3 years instead of 6kg for adherers and 0.4 in the control group) to be switched to therapeutic treatment (metformin) after 12 months, thus increasing gains for adherers and non adherers alike compared to what appears in trials. Overall, their LS intervention is CE, based on UK costs. Allowing for switches to metformin for non adherers, it even becomes cost saving. • It is pure modeling, as no trials are available in the UK. For efficacy of the intervention (proportion cases prevented) they use the DPS, a Finnish study: it found a reduction in cumulative incidence at 4 years from 23% to 11% and at 8 years from 38% to 23%. They project cumulative incidence at 20 years starting from the value at 8 years observed in the DPS and adding an exponential declining curve. In the control group, cumulative incidence plateaus at about 70% at 20 years. • They add the Sheffield T2DM model to predict the onset of co-morbidities (retinopathy, nephropathy, neuropathy, CHD and CVD) and they cost them through micro-costing exercises. The intensive intervention lasts 4 years and is followed by light reminders and costs per year (from 1 to 4) are derived from those observed in the DPS (unit costs observed in the UK applied to volumes observed in the DPS).

	• They assume levels of adherence for the intervention (responders, at 40% at 4 years and 60% at 12 months) and the metformin treatment. • They estimate a gain in HRQoL based on changes in clinical outcomes (BMI, blood pressure) for which they are known and find that the intervention yields on average a gain of 0.066. • They find a cost per QALY of £1,800 or approximately $3,500, in the base-case scenario (non adherers not allowed to quit); net cost of the intervention is £121 for a gain of 0.066 units of QALY. When non adherers can switch to metformin, the intervention becomes cost-saving. • They also have an interesting discussion of when to start the intervention (pre-diabetes, IFG, diabetes?)

5. **Herman, W. H., Edelstein, S. L., Ratner, R. E., Montez, M. G., Ackermann, R. T., Orchard, T. J., … Diabetes Prevention Program Research Group. (2013).** Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. *The American Journal of Managed Care*, *19*(3), 194–202.

Study type	Cost effectiveness: Drugs and Weight Loss
Notes	10-year follow up (3 years RCT + 7 years open label). Lifestyle intervention involving 5% loss of bodyweight (to be deemed an adherer), non adherers are shifted to a metformin treatment. Placebos receive nothing. Risk decreases by 50% among adherers (cumulative incidence at 10 years) versus placebo and 21% for metformin.
	ICER: with a 3% TDR, $20,000 LS versus placebo from perspective of health care system and $4,200 if societal perspective.
	Metformin versus placebo is cost-saving from a societal perspective and is $20,200 from a health system perspective.
	LS versus metformin is $19,700 per QALY-gained.
	It is not easy to compare ICER across three strategies: I(LSvM) = I(LSvP)+(Q(M)-Q(P))/(Q(LS)-Q(M))(I(LSvP)-I(MvP)). Because I(LSvP)-I(MvP) is very close to 0, I(LSvM) is very close to I(LSvP).
	LS costs $25,600 per QALY versus metformin from societal perspective.
	Seems to be similar to DPP- check why ICER are higher.

6. **Herman, W., & The Diabetes Prevention Program Research Group. (2012).** The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention An intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care*, *35*(4), 723–730. doi:10.2337/dc11-1468

Study type	Cost effectiveness: Drugs Versus Lifestyle
Notes	Same as 5 except that non adherers cannot switch to metformin

7. **Irvine, L., Barton, G. R., Gasper, A. V., Murray, N., Clark, A., Scarpello, T., & Sampson, M. (2011).** Cost-effectiveness of a lifestyle intervention in preventing Type 2 diabetes. *International Journal of Technology Assessment in Health Care*, *27*(4), 275–282. doi:10.1017/S0266462311000365 [restricted access]

Study type	Randomized Control Trial
Notes	An intervention targeted to pre-diabetic (IFG) or recently diagnosed patients – group education, physiotherapy and peer support. N=177, 7 months. Overall ICER at 7 months (within trial) is £67,000, not CE. Restricted to IFG patients only, ICER is £20,000, or CE.

8. **Lawlor, M. S., Blackwell, C. S., Isom, S. P., Katula, J. A., Vitolins, M. Z., Morgan, T. M., & Goff, D. C. (2013).** Cost of a group translation of the Diabetes Prevention Program: Healthy Living Partnerships to Prevent Diabetes. *American Journal of Preventive Medicine*, *44*(4 Suppl 4), S381–389. doi:10.1016/j.amepre.2012.12.016

Study type	Randomized Control Trial: Weight Loss/Education
Notes	LS intervention to lose weight through education. Participants in intervention lost 7% bodyweight. N=301, conducted 2007-11, over 2 years for each participant. The intervention is cost-saving ($1,800 per participant over the course of 2 years)

9. **Lohse N, Marseille E, Kahn JG.** Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. International Journal of Gynecology and Obstetrics. 2011;115(Supplement 1):S20-S25.

Study type	computer simulation model (GDModel) cost-effectiveness of various GDM screening and management strategies
Notes	LS intervention to lose weight through education. Participants in intervention lost 7% bodyweight. N=301, conducted 2007-11, over 2 years for each participant. The intervention is cost-saving ($1,800 per participant over the course of 2 years)
	It is about ILC intervention (following systematic screening of all pregnancies for GDM) to prevent T2DM. GDM causes 30% of T2DM. The intervention is CS in India and Israel. Sensitivity analysis shows that the intervention remains CS in Israel but becomes CE in India. However the ICER is still very low (lower than GDP per capita, which is the WHO threshold).
	Mathematical modeling, lifetime horizon, perspective of the health care system. Efficacy (Delta incidence): 58%. The ILC decreases the risk to develop T2DM dramatically among pregnant women with GDM.
	TDR: 3% for costs (TDR not mentioned for outcomes)

	T: they take the median lifetime cost of treatment of T2DM in the US at $88,000 and divide by 67.7, or $1,300, to get the cost in India (3.3, or $26,700 in Israel). Their source is the CORE model and they inflate costs by 5% per year to 2011 (A Markov model of complications developed in 2004). Total costs are bottom up, not regression.
	C is super low: $10 to $50 in India and $100 in Israel.
	Because they find the intervention to be CS they do not calculate any ICER but they measure the impact on DALYs. Note: DALY is different from QALY is that it is a burden measure, it adds YLL to YLD, relative to a maximum of LEWD (Life Expectancy Without Disability). QALY is a positive measure and does not depend on life expectancy.

10. **Neumann, A., Schwarz, P., & Lindholm, L. (2011).** Estimating the cost-effectiveness of lifestyle intervention programmes to prevent diabetes based on an example from Germany: Markov modelling (Structured abstract). *Cost Effectiveness and Resource Allocation*, *9*(17).

Study type	Markov model: Nutrition, Exercise
Notes	Societal perspective, lifetime horizon, Markov model of nutrition interventions. They are low cost but also low effectiveness. Interventions are cost-saving among middle-aged adults (30 to 50), and ICER = 20,000 (women) to 30,000 (men) Euros for those aged 70+.

11. **Palmer, A., & Tucker, D. (2012).** Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis (Provisional abstract). *Primary Care Diabetes [restricted access, check I can access through Mac]*, *6*(2), 109–121.

Study type	A semi-Markov, 2nd-order Monte Carlo model: Lifestyle including medication and education
Notes	Markov simulation of lifetime costs and gains of an intervention targeted toward overweight and obese individuals with IGT, from a 3rd party payer's perspective in Australia. Metformin costs AUS$10,000 per QALY and intensive LS intervention is cost saving. Four states are simulated (normal, IGT, T2DM, and death). Intervention costs are derived from DPP for the first three years and 0 after year 4. T (cost of T2DM) is estimated at AUD3,000 per year (table 1, page 111: total cost of T2DM is AUD5,000, but normal glucose regulation and IGT also have costs of treatment and the difference between T2DM and these groups is 3,000 only (approximately 40% of the cost of T2DM). Gains in QALY are quite large, at 0.02 per year in the ILC group (Intensive Lifestyle Change). The main reason the ICER is so low is because they make the assumption of no catching up at all after 4 years: once the intervention is over, individuals in the ILC arm remain approximately at the same rate of progression from IGT to T2DM as those in the control group. It is pure delay (if delays initially by five years, the five years are kept after the intervention is over).

12. **Sagarra, R., Costa, B., Cabré, J. J., Solà-Morales, O., & Barrio, F. (2014).** Lifestyle interventions for diabetes mellitus type 2 prevention. *Revista Clínica Española (English Edition)*, *214*(2), 59–68. doi:10.1016/j.rceng.2013.11.003

Study type	Cost effectiveness: Standardized vs Intensive Lifestyle Intervention
Notes	Prospective cohort in Catalonia, n=552 high risk patients (for diabetes). An intensive structured 6 hours teaching lifestyle change intervention decreases 4.2 year cumulative incidence from 29% (control, standard care) to 18%, yielding an ICER of € 3,243 at 4 years.

13. **Saha, S., Gerdtham, U.-G., & Johansson, P. (2010).** Economic Evaluation of Lifestyle Interventions for Preventing Diabetes and Cardiovascular Diseases. *International Journal of Environmental Research and Public Health*, *7*(8), 3150–3195. doi:10.3390/ijerph7083150

Study type	Cost effectiveness: Physical Activity and Exercise
Notes	This is a systematic review of 46 economic studies of lifestyle interventions to reduce the incidence of T2DM and/or CVD.
	They identify 46 studies/interventions: 12 DPP like (ILC), 6 exercise, 5 diet, 14 diet+exercise, and 9 ILC+drug. 9 of the 12 DPP studies are CUA, as well as 3 of the exercise, 2 of the diet, 8 of the exercise+diet, and all the 9 ILC+drug, or a total of 31 CUA, most of them calculating cost per QALY. Only 16 are CUA from the Healthcare System (HCS) perspective (15 are societal or unclear perspective). Last, 5 only are CUA from the HCS perspective of DPP-like interventions (3 use standard care as the comparator and 2 no intervention at all). Of these, they find the following results: 1. Ackerman, 2006, versus standard care, ICER = $2,000 in the US 2. DPP-RG, 2003, versus standard care, not clear (they only provide the societal ICER at $60,000 in the US). 3. Eddy, 2005, versus no intervention 4. Herman, 2005, versus standard care, ICER = $1,100 in the US 5. Hoerger, 2007, versus no intervention, ICER = $10,000 in the US
	The following paragraph: “Methodological disagreement is the main issue in DPP-like studies. The results of DPP interventions are reported as 8,800 US$/QALY or 62,600 US$/QALY depending on whether a Markov [38] or Archimedes model [44] is applied. If 50,000 US$/QALY is considered a cutoff value for cost-effectiveness, the same trial is cost-effective with one method but not the other. The disagreement stems from different model assumptions on the rates of progression to diabetes and complications [49,50]. Both authors provide arguments and counterarguments defending their assumptions [51,52].” is wrong. The first three sentences are true but the last one does not identify the source of the disagreement correctly: Eddy, 2005, predicts a very high ICER simply because they overestimate the cost of the intervention. It is true that studies based on Markov models are

	too optimistic with regard to the gains in cumulative incidence, and Archimedes is certainly better from an epidemiological perspective, but Eddy and Shlessinger did not do the economic evaluation correctly. The review discusses mostly effectiveness (DAM versus Archimedes and long-term adherence) but misses the issues surrounding estimates of C, T, and Q
	Studies vary along many dimensions: type of intervention (12 lifestyle interventions, 6 physical activity, 5 dietary changes, 14 combinations of dietary and physical, and 9 including a drug plus any of the above), comparator (placebo, standard, drug alone), target groups (by age and risk factors), settings (national or local), countries (mostly high income), time discount rates (some studies use different TDRs for costs and benefits), time horizons, outcomes (CCA, CEA, CUA, or CBA) and methods (6 decision trees, 21 Markov models, one combination of DT and Markov, 2 life-tables, and one Archimedes).
	Modeling is needed to go from a short-term follow up (clinical trial, usually no more than 2 years, often less) to lifetime or long-term (30 years) differences in costs and benefits between treated and control, the reason being that prevention of T2DM will have economic effects long in the future. It is therefore a question of predicting outside of the sample. Archimedes is an event-driven, continuous model simulating underlying changes in physiologic processes to create health states (such as T2DM) whereas Markov models are time-driven and discrete (in time and states). The same intervention (and clinical trial, DPPM) is modeled using a Markov and the Archimedes model, yielding diametrically opposed conclusions: the lifestyle intervention at onset (at the IGT stage) costs $63K per QALY according to the Archimedes model, but $9K only according to Markov. The drug intervention (metformin at the IGT stage) costs $35K/QALY according to Archimedes but $30K/QALY only according to Markov. Last, Archimedes evaluates lifestyle at T2DM onset and finds a cost of $25K/QALY only (no evaluation based on the Markov model). Engelgau (2005) compares the two models and concludes that Archimedes over-estimates the ICER due to a shorter horizon (30 years instead of death) but also due to underlying assumptions on micro-vascular complications (parameters entered in the model underestimate these rates compared to observed). This is interesting because the model has been validated on its outcomes for the duration of the trial, which, obviously, does not mean that all parameters are correct.
	Another thorny issue is that of unrelated costs of prolonging a life: if T2DM is prevented, the individual will be more likely to suffer from dementia (Rappange et al., 1998). Here, bring in the findings from Goldman et al. (2005), they have something on diabetes prevention. Most studies do not model these unrelated medical costs.
	Use the raw data in this article to try and understand the effects of some values of the parameters (see Anderson, 2012).
	Overall, their conclusion is that lifestyle interventions are in the cost-effective range (except when estimated based on the Archimedes model) but conclusions are less convincing for the other four types of interventions.
	Some interventions include pre-screening and intervening on positive cases only.
	<u>Discussion of merits and flaws of Archimedes versus Markov:</u>

	Brandeau, M.L. Modeling Complex Medical Decision Problems with the Archimedes Model. Ann. Intern. Med. 2005, 143, 303–304. Engelgau, M.M. Trying To Predict the Future for People with Diabetes: A Tough but Important Task. Ann. Intern. Med. 2005, 143, 301–302. Reference to an older (2006) SR of health economics of prevention in T2DM: Vijgen, S.M.C.; Hoogendoorn, M.; Baan, C.A.; de Wit, G.A.; Limburg, W.; Feenstra, T.L. Cost Effectiveness of Preventive Interventions in Type 2 Diabetes Mellitus: A Systematic Literature Review. Pharmacoeconomics 2006, 24, 425–441.
	Other dimensions explaining variability in ICER: • **The timescale of the modelling**. Some studies examined cost-effectiveness only during the duration of a trial, and these give far higher ICERs than studies that adopt a 20-year or lifetime approach. The underlying problem here is the need to extrapolate from short trials to lifetimes. • Different costings, and in particular **whether the cost of screening was included** in the cost of prevention of diabetes. Icks et al. (2007) 263 estimated that 36% of the cost came from the screening. • Different assumptions on **duration of benefit**, with pessimists assuming that the benefit would end when the intervention did and optimists assuming that they would last for life. Modelling based on the DPS might assume some prevention of diabetes, modelling based on the DPP might assume just a delay. • Different assumptions about **adherence** in 'real-life' settings. Icks et al. (2007) 263 assumed that the cost-effectiveness of a DPP-style intervention would be less in routine care because adherence to lifestyle measures would be poorer and shorter. • Assumptions about **costs of interventions**. For example, delivering the DPP intervention in groups considerably reduced the ICER. Some studies used costs based on those in the trial, whereas others based costs on national health-care cost databases. • Different **timings** of studies. For example, those studies that were carried out before generic statins became available produced higher ICERs. • Different methods for **estimating QALYs**.

14. **Vojta, D., Koehler, T. B., Longjohn, M., Lever, J. A., & Caputo, N. F. (2013).** A coordinated national model for diabetes prevention: linking health systems to an evidence-based community program. *American Journal of Preventive Medicine*, *44*(4 Suppl 4), S301–306. doi:10.1016/j.amepre.2012.12.018

Study type	Economic Scaling Intervention
Notes	Business case for scaling up LS interventions in the US. No ICER.

15. **Wier, M. F. van, Lakerveld, J., Bot, S. D. M., Chinapaw, M. J. M., Nijpels, G., & Tulder, M. W. van. (2013).** Economic evaluation of a lifestyle intervention in primary care to prevent type 2 diabetes

mellitus and cardiovascular diseases: a randomized controlled trial. *BMC Family Practice*, *14*(1), 45. doi:10.1186/1471-2296-14-45

Study type	Randomized Control Trial: Usual Care versus Lifestyle Counselling (Diet/Exercise)
Notes	I may not understand how this works, but it seems really poorly done and I would not use any of their conclusions. They piggyback on an RCT conducted in several family practices in the Netherlands in which 350 participants were randomly assigned to a treatment consisting of six face-to-face counseling sessions on lifestyle (smoking, exercise, or diet) and three phone sessions, and 350 to a control group receiving a brochure only.
	The main outcome measure is a measure of a 9-year risk of developing T2DM: The 9-year risk of developing T2DM was estimated with the risk formula derived from the Atherosclerosis Risk In Communities (ARIC) Study, based on ethnicity, parental history of diabetes, systolic blood pressure, waist circumference, and height [ref: Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, et al: Identifying individuals at high risk for diabetes: the atherosclerosis risk in communities study. Diabetes Care 2005, 28:2013–2018.]. Overall, the treatment does not change anything (if any difference is seen it is in favour of the control, and all ICERs are located in the West half of the CE graph, or non-effective). Then, they use costs: the cost of the intervention results from micro-costing (nurses reported on each visit or phone consultations and volume is simply multiplied by the unit cost of each). It is EUR98.00. So, the intervention costs almost EUR100.00 for no impact. But the authors do not stop here: they compare health care costs, participants costs (complementary care, over-the-counter (OTC) medication, and costs associated with improving physical activity, such as sports club memberships and sports equipment), and productivity losses across the two groups and find that costs are lower in the intervention group (mostly in productivity loss, where controls lose EUR729 more than interventions). They use this result to conclude that the intervention is cost saving and then embark on calculating a negative ICER, which is of course very negative because the change in QALY is almost 0. This, to me, is total nonsense. First, if the intervention saves cost, why calculate an ICER???? Second, how come the intervention saves cost, especially productivity losses: would they suggest that receiving counseling makes one less sick, even though it cannot change the risk of developing T2DM at nine years. Retrieve the ARIC formula.

Screening and Prevention

1. **Bertram, M. Y., Lim, S. S., Barendregt, J. J., & Vos, T. (2010).** Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. *Diabetologia*, *53*(5), 875–881. doi:10.1007/s00125-010-1661-8

Study type	Cost effectiveness: Opportunistic Screening followed by Lifestyle intervention
Notes	Starts with screening by physicians in general practice of all eligible individuals: : age >55 years; or age >45 plus high BMI, family history of type 2 diabetes or hypertension; or people

	from 'high-risk' groups (e.g. Indigenous Australians and women who suffered from gestational diabetes).
	Then those detected with pre-diabetes are offered one of six (three lifestyle: diet, exercise, diet+exercise, and three therapeutic) interventions. Horizon = lifetime. Perspective = health care system, but without cost-avoidance (no estimates of T). Results: CER of AU$23,000 per DALY for the intensive LS intervention (diet+exercise, 3 years).
	Method: Markov, three diabetes-related states (normal, pre, diabetes, pre being reversible, but diabetes being absorbing) and 3 complications (Stroke, CVD, renal disease). DALY gained estimated based on review of literature.
	Overall, it is similar to interventions studied above, as the screening is opportunistic (during regular GP visits).

2. **Castro-Rios, A., Doubova, S., Martinez-Valverde, S., Coria-Soto, I., & Perez-Cuevas, R. (2010).** Potential savings in Mexico from screening and prevention for early diabetes and hypertension (Provisional abstract). *Health Affairs*, *29*(12), 2171–2179.

Study type	Cost saving analysis: Preventive care and Screening
Notes	Horizon = 20 years
	Perspective = health care system only (no indirect costs)
	The cost of screening *per se* is very low, therefore the analysis is the same as evaluating the LS intervention (as conducted above). They make strong assumptions (e.g., the intervention delays onset of diabetes by 5 years and all pre-diabetics become diabetics in 5 years). It is not clear how T is evaluated but cost differentials are small in general (less than 10%).

3. **Chatterjee, R., Narayan, K. M. V., Lipscomb, J., Jackson, S. L., Long, Q., Zhu, M., & Phillips, L. S. (2013).** Screening for Diabetes and Prediabetes Should Be Cost-Saving in Patients at High Risk. *Diabetes Care*, *36*(7), 1981–1987. doi:10.2337/dc12-1752

Study type	Cost comparison: Screening
Notes	Screening and metformin, not prevention. All strategies but indiscriminate screening are CS, the most one being targeting obese patients (reduces costs by 19%). Not clear how routine costs were calculated, but, once again, costs of screening are low compared to costs of treatment or intervention.

4. **Chatterjee, R., Narayan, K. M. V., Lipscomb, J., & Phillips, L. S. (2010).** Screening Adults for Pre-Diabetes and Diabetes May Be Cost-Saving. *Diabetes Care*, *33*(7), 1484–1490. doi:10.2337/dc10-0054

Study type	Cost comparison: Screening
Notes	

5. **Chen, L., Magliano, D. J., Balkau, B., Wolfe, R., Brown, L., Tonkin, A. M., … Shaw, J. E. (2011).** Maximizing efficiency and cost-effectiveness of Type 2 diabetes screening: the AusDiab study. *Diabetic Medicine*, *28*(4), 414–423. doi:10.1111/j.1464-5491.2010.03188.x

Study type	Cost effectiveness: Screening
Notes	This is a comparison of four screening strategies, based on cost per case detected. The best strategy in the Australian context is to run a test based on self-assessed measures on the whole population, then measure FPG on those identified as high risk by the first test (AUSDRISK1), and, finally, recalculating risk with a second tool called AUSDRISK2. Three strategies using AUSDRISK1 in the first step are comparable in cost per case detected, the only clearly dominated strategy being to perform FPG on the whole population, without stratifying on the basis of AUSDRISK1. The combined screening + ILC cost per QALY falls between AUD10,000 and AUD14,770 assuming 30% reduction in incidence of T2DM and with various rates of reversion from T2DM to pre-diabetes (from 0% to 30%). No cost avoidance, horizon is within trial.

6. **Johansson, P., Ostenson, C. G., Hilding, A. M., Andersson, C., Rehnberg, C., & Tillgren, P. (2009).** A cost-effectiveness analysis of a community-based diabetes prevention program in Sweden (Provisional abstract). *International Journal of Technology Assessment in Health Care*, *25*(3), 350–358.

Study type	Cost effectiveness: Screen Detected, Diet and Exercise
Notes	This is a prevention ILC program, not screening. Societal perspective. Horizon = 10 years. The program is not always effective in QALYs (loss of QALYs in some intervention sites relative to control site). Note, it is quasi-experimental, as the randomization applies to sites not individuals.

7. **Kahn, R., Alperin, P., Eddy, D., Borch-Johnsen, K., Buse, J., Feigelman, J., Wareham, N. J. (2010).** Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *The Lancet*, *375*(9723), 1365–1374. doi:10.1016/S0140-6736(09)62162-0

Study type	Cost effectiveness: Screening

Notes	Horizon = 50 years. Simulation based on **Archimedes** of nine screening strategies (parameters are: initiation, can be age at 30, 45, or 60 or blood pressure, at 140/90 or 135/80; frequency in years, from six months to 5 years). All stop at age 75. Once diagnosed the individual receives treatment based on consensus (insulin, metformin, ILC, Nathan et al. Diabetes Care, 2009), which prevents complications and, for some, helps regression to pre-diabetes. All strategies are cost-effective, the best being to screen all individuals with blood pressure greater than 140/90 every year (CER = USD6,300). Assumes perfect compliance with the test when ordered.

8. **Khunti, K., Gillies, C. L., Taub, N. A., Mostafa, S. A., Hiles, S. L., Abrams, K. R., & Davies, M. J. (2012).** A comparison of cost per case detected of screening strategies for Type 2 diabetes and impaired glucose regulation: Modelling study. *Diabetes Research and Clinical Practice*, *97*(3), 505–513. doi:10.1016/j.diabres.2012.03.009

Study type	Cost comparison: Screening
Notes	Cost per case detected is about £450 (USD675) for the best strategy (risk stratification tool based on self-assessment followed by blood test.
	All screening strategies are CS. The best per test performed is to target those with BMI>35 or SBP>130. The highest level of total cost saving is screening all.

9. **Mehrotra, S., & Kim, K. (2011).** Outcome Based State Budget Allocation for Diabetes Prevention Programs Using Multi-criteria Optimization with Robust Weights. *Health Care Management Science*, *14*(4), 324–337.

Study type	Budget allocations
Notes	Not relevant (interesting though)

10. **Mortaz, S., Duncan, Gray, Badawi, A., & Wessman, C. (2012).** Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: a Markov model simulation. *ClinicoEconomics and Outcomes Research*, 91. doi:10.2147/CEOR.S30547

Study type	Markov model: Screening
Notes	Important paper for us: compares three screening strategies (every year, every 3, every 5 years, for at risk individuals, aged 40 and older, targeting following the ADA recommendations (older than 40, or family or ethnicity or overweight/obesity, or symptoms of T2DM). Those detected receive treatment: DPP-style ILC if detected with pre-diabetes to prevent T2DM, and insulin control if detected with diabetes to control complications. All strategies (1, 3, or 5 years) are cost saving for a cohort of individuals at risk of developing T2DM and improve QALYs. It is hard to compare to other studies, however, as it lumps

	together pre-diabetes prevention and prevention of complications of diabetes. In the simulation, IFG and T2DM are both absorbing states
	T (cost of treatment if sick): They use a value of $5,700 per year for T2DM with complications and $2,210 for T2DM without.
	Q: gains are close to base-case scenario in Henderson (around 0.3) compared to no screening (no treatment).
	Best strategy is every 5 years.

11. **Pereira Gray, D. J., Evans, P. H., Wright, C., & Langley, P. (2012).** The cost of diagnosing Type 2 diabetes mellitus by clinical opportunistic screening in general practice. *Diabetic Medicine*, *29*(7), 863–868. doi:10.1111/j.1464-5491.2012.03607.x

Study type	Cost analysis: Opportunistic Screening
Notes	Observational (retrospective) study of administrative records in a UK region with mentions of diagnostic tests for T2DM. Finds an average cost of BRP377 per case detected.

12. **Schaufler, T. M., & Wolff, M. (2010).** Cost Effectiveness of Preventive Screening Programmes for Type 2 Diabetes Mellitus in Germany. *Applied Health Economics and Health Policy*, *8*(3), 191–202.

Study type	Markov Monte Carlo micro-simulation model: Screening and Prevention strategies
Notes	Markov micro-simulation of lifetime costs and benefits of screening. Risk reduction of T2DM in the ILC and metformin arms are taken from DPP and risk reductions for complications from UKDPS. Gains in QALY are huge (close to 3 over the lifetime: given life expectancy at diagnosis is 21 years, this would represent 0.15 QALY gained per year, which seems fine (0 initially to 0.29 in final years). The CER is very low (less than 1,000 EUR per QALY) for those already diagnosed with T2DM and both prevention interventions (ILC and metformin) are C-S among those with IFG or IGT.

13. **Thurecht, L., Brown, L., & Yap, M. (2011).** Economic Modelling of the Prevention of Type 2 Diabetes in Australia--The Diabetes Model. *International Journal of Microsimulation*, *4*(3), 71- 80.

Study type	Diabetes projection model
Notes	No costs.

14. **Waugh, N. R., Shyangdan, D., Taylor-Phillips, S., Suri, G., & Hall, B. (2013)**. Screening for type 2 diabetes: a short report for the National Screening Committee. *Health Technology Assessment (Winchester, England)*, *17*(35), 1–90. doi:10.3310/hta17350

Study type	Health Technology Assessment
Notes	Not CE, mostly effectiveness, but no ICER per se (the reason being that most screening are not effective to start with).

Both

1. **Li R., Zhang P., Barker L.E., Chowdhury F.M., & Zhang X. (2010).** Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review. *Diabetes Care*, *33*(8), 1872–1894.

Study type	Systematic Review and Cost effectiveness
Notes	56 studies of CE of interventions recommended by the American Diabetes Association (ADA) to prevent diabetes or its progression and complications. Studies were published in English between 1985 and May 2008, from 20 countries. This SR follows the Cochrane Collaboration Recommendations and assessed interventions recommended by the ADA only. Includes T1DM, T2DM and GDM (we are only interested in T2DM). Also includes population-based ecological prevention interventions whereas we are interested in targeted (toward patients at risk of developing T2DM) interventions only. Used the BMJ's authors guide 13 items quality assessment to evaluate the quality of studies and included those of good or excellent. All costs are converted in 2007 USD using the foreign exchange rate at the time of the study (relative to the USD of the same period) and the US consumer price index to convert costs to the year 2007. Therefore, no allowances are made for Purchasing Power Parities when comparing across countries. ICERs are calculated for years of life gained, adjusted for quality or not (some studies are in life years only while other studies add quality and calculate QALY gains.) The perspective is that of the health care system as a whole (all direct medical costs, whether covered or not by the public insurer). • 104 studies were retrieved, 6 were excluded due to insufficient quality, 27 because they were not about ADA recommended interventions, and 15 because they failed to provide outcomes in QALY or LY-g, leaving 56 studies in the set. Note: 14 foreign-language studies were excluded independent of quality, outcome measure or type of interventions. • 39 of these studies simulate the long-term costs and effects of the intervention (25 years to lifetime). • These 56 studies cover various broad groups of interventions (note: 8 publications cover two interventions and one covers 3; as a result, 66 studies are mentioned below):
	Most studied to least studied interventions: 1. **ESRD**: The most-studied type of intervention is the prevention of end-stage renal disease (ESRD) through prescription of Angiotensin-Converting Enzyme (ACE) inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB), with 17 studies . 2. Intensive **glycemic control** (12 studies) 3. Lifestyle changes interventions to **prevent T2DM among high risk patients** (8 studies) 4. **Control cholesterol levels** through prescription of Statin: 5 studies 5. **screening to prevent retinopathy**: 5 studies 6. **Intensive hypertension control:** 4 studies

	7. **Screening** T2DM or GDM (gestational DM): 3 studies 8. **Diabetes education programs:** 2 9. **Diabetes disease management:** 2 10. **Optimal foot care**, 2 11. **Comprehensive interventions:** 2 12. **Self-monitoring of blood glucose**: 1 13. **Smoking cessation**:1 14. **Foot care**: 1 15. **Eye care:** 1
	Studies are grouped by interventions and the unit of observation in the statistical analysis is the intervention, not the study. An intervention is supported by strong evidence if one study rated as "excellent" supports it, or more than one studies rated as "good". If more than one study support the evidence the estimated ICERs must be similar.
	26 specific interventions are classified as supported by strong evidence and 18 interventions are classified as supported by supportive rather than strong evidence. Of these 44 interventions, 38 are cost-saving or cost less than $50,000 per life year (or QALY), which would make them cost-effective almost everywhere and 6 only cost more than that threshold per QALY.
	Findings of interventions with strong evidence (n=26): **Cost-saving**: None out of the six studies with strong evidence showing the intervention to be cost-saving are concerned with the prevention or screening of T2DM (they are concerned with the prevention or detection and early treatment of complications of diabetes). **Very cost-effective** (ICER below $25K, n=8): one is concerned with prevention of T2DM through ILC and one with screening among African-Americans 45 to 54 years old. **Cost-effective** (25<ICER<50, n=6): One is concerned with screening and/or prevention of T2DM, the one-time opportunistic targeted screening for undiagnosed type 2 diabetes in hypertensive persons aged 45 years and older compared with no screening.
	So, overall, interventions to prevent complications or incidence of diabetes seem to be cost-effective. Excluding interventions not targeted to T2DM (T1DM and GDM), a large majority is still cost-effective (8 cost-saving, 11 cost less than 25,000 per QALY, and 5 between 25,000 and 50,000) versus 6 non cost-effective (2 at 50,000 to 100,000 per QALY and 4 at more than 100,000 per QALY).
	What is not cost effective (more than $50,000 per QALY)? • Intensive glycemic control (versus conventional) among newly diagnosed T2DM (targeting the 55-94 year-olds is not CE but including all ages is marginally CE, which is paradoxical – dig deeper). (2 interventions) • Increasing the frequency of eye screening from every 2 years to every year or from every 3 to every 2 years. (2 interventions) • Universal opportunistic screening of the whole population aged 45 and older, versus targeted screening of the population aged 45 and older with hypertension.

	• Universal opportunistic screening of the whole population aged 45 and older followed by appropriate treatment versus no screening at all.

The table below summarizes the findings: columns distinguish between prevention of complications once T2DM has been diagnosed and rows distinguish between interventions that are cost-saving, very CE, CE, and not CE. Overall, many more studies of prevention of complications have been carried out than studies of screening (six only, versus 24 for prevention).

Cost	Prevention of complications	Screening
Cost-saving	ACEI for hbp; ACEI+ARB for ESRD; public coverage of ACEI; drug to control hbp at micro-albuminial stage; Prevention of foot ulcer; {education, screening, ACEI}; Intensive treatment of foot ulcer.	Mobile device for retina (versus specialist visit)
<$25K/QALY	Lifestyle change (nutrition) (*); Glycemic control as in the UKPDS; statin targeted to patients with hyperlipidemia and CVD history; quit smoking (*); treat retinopathy; self-management; Self-management blood glucose (3 times or one time a day)	All African-Americans aged 25 to 54 (2 interventions: 25 to 44 and 45 to 54)
25 to 50K/QALY	Glycemic control US setting ages 25-54 (*); statins for patients with hyperlipidemia but no history of CVD; metformin (treatment for obese people)	All 45+ with hypertension (**)
>50/QALy	Glycemic control US setting all ages above 25.	Increase frequency of eye screening by one year; universal opportunistic screening all aged 45+ (versus hypertensive); universal opportunistic screening + treatment for all 45+.

(*) Wide range: lifestyle intervention is between cost-saving and a cost of $84,000 per QALY; smoking cessation programs between less than 25,000 and 90,000; glycemic control for the 25-54 is between 14,000 and 56,000

(**) Wide range of estimates (47,000 to 71,000) and median close to 50,000

Economic Calculation Tables

Simulations

						Number of cases averted 20 year follow up					
	C	T	Q	W	A	Observed	Archimedes	Markov	Score (situations where it is CE)		
3 year intervention	49,768,658,928	56,371	0.29	50,000	702,243	1,736,427	1,549,427	2,671,426	3		
6 year intervention	87,475,831,272	56,371	0.29	50,000	1,234,297	1,736,427	1,549,427	2,671,426	3		
6 year, adjusted	77,853,489,832	56,371	0.29	50,000	1,098,524	1,736,427	1,549,427	2,671,426	3		
10 year intervention	137,752,061,064	56,371	0.29	50,000	1,943,701	1,736,427	1,549,427	2,671,426	1		
10 year adjusted	106,069,087,019	56,371	0.29	50,000	1,496,650	1,736,427	1,549,427	2,671,426	3		
	Intervention cost:	Treatment cost	QALY gained	WTP	Number cases						
	LS to all pre-diab	per person	per person	per QALY	To be prevented						
	adjusted:	Base-case (Archimedes)	Base-case (Archimedes)	Most-conservative	to reach CE						
	minus pre-diab to diab				A=C/(T+QW)						

ICER					ICER		
	C	T	Q	W	Observed	Archimedes	Markov
3 year intervention	49,768,658,928	56,371	0.29	50,000	-95,550	-74,616	-200,218
6 year intervention	87,475,831,272	56,371	0.29	50,000	-20,669	264	-125,337
6 year, adjusted	77,853,489,832	56,371	0.29	50,000	-39,778	-18,844	-144,445
10 year intervention	137,752,061,064	56,371	0.29	50,000	79,172	100,105	-25,496
10 year adjusted	106,069,087,019	56,371	0.29	50,000	16,254	37,188	-88,414

Base-case Q and Canadian T (Dawson et al 2002)											
						Number of cases averted 20 year follow up					
	C	T	Q	W	A	Observed	Archimedes	Markov	Score (situations where it is CE)		
3 year intervention	49,768,658,928	27,007	0.29	50,000	1,199,037	1,736,427	1,549,427	2,671,426	3		
6 year intervention	87,475,831,272	27,007	0.29	50,000	2,107,486	1,736,427	1,549,427	2,671,426	1		
6 year, adjusted	77,853,489,832	27,007	0.29	50,000	1,875,662	1,736,427	1,549,427	2,671,426	1		
10 year intervention	137,752,061,064	27,007	0.29	50,000	3,318,751	1,736,427	1,549,427	2,671,426	0		
10 year	106,069,087,019	27,007	0.29	50,000	2,555,438	1,736,427	1,549,427	2,671,426	1		

adjusted											
	Intervention cost:	Treatment cost	QALY gained	WTP	Number cases						
	LS to all pre-diab	per person	per person	per QALY	To be prevented						
	adjusted:	Base-case (Archimedes)	Base-case (Archimedes)	Most-conservative	to reach CE						
	minus pre-diab to diab				A=C/(T+QW)						

ICER					ICER		
	C	T	Q	W	Observed	Archimedes	Markov
3 year intervention	49,768,658,928	27,007	0.29	50,000	5,705	15,734	-44,441
6 year intervention	87,475,831,272	27,007	0.29	50,000	80,585	90,614	30,439
6 year, adjusted	77,853,489,832	27,007	0.29	50,000	61,477	71,506	11,331
10 year intervention	137,752,061,064	27,007	0.29	50,000	180,426	190,455	130,280
10 year adjusted	106,069,087,019	27,007	0.29	50,000	117,509	127,538	67,363

Conservative Q and W but base-case T							
ICER					ICER		
	C	T	Q	W	Observed	Archimedes	Markov
3 year intervention	49,768,658,928	56,371	0.16	50,000	-173,184	-135,242	-362,894

6 year intervention	87,475,831,272	56,371	0.16	50,000	-37,463	479	-227,173
6 year, adjusted	77,853,489,832	56,371	0.16	50,000	-72,097	-34,155	-261,807
10 year intervention	137,752,061,064	56,371	0.16	50,000	143,498	181,441	-46,212
10 year adjusted	106,069,087,019	56,371	0.16	50,000	29,460	67,403	-160,250

Economic direct cost in Canada			Cost per person							
	Stock (prevalence)	Total Direct Cost	Year	Per person	Inflated 2013					
Dawson et al. 2002	1,296,048	2,627,000,000	1998	2,027	2,728	Method: attributable fractions (underestimate)				
EBIC 2008		2,178,000,000	2007	1,680	1,893	Method: by diagnostic category on DAD, and physician services and drugs				
Katzmarzyk, 2000		620,000,000	1999	478	631	Method: EBIC 1993 inflated to 1999				
						Note: EBIC 2008 uses RIW for inpatient, whereas EBIC 1993 uses per diem.				
Caro et al. 2004			2003	11,624	14,170	Micro-costing of all events associated with T2DM				
Simpson et al. 2003	38,000	134,000,000	1996	3,526	4,938	Micro-costing of events, individual-level data from SK				
Anis et al. 2009		1,413,800,000	2006	1,091	1,253	Top down from NHEX, using weights per morbidity calculated by EBIC 1998				

Base-case Q and true base-case T (net cost: diabetes minus pre-diabetes, from Eddy et al. 2005)									
						Number of cases averted 20 year follow up			

	C	T	Q	W	A	Observed	Archimedes	Markov	Score (situations where it is CE)		
3 year intervention	49,768,658,928	30,997	0.29	50,000	1,093,891	1,736,427	1,549,427	2,671,426	3		
6 year intervention	87,475,831,272	30,997	0.29	50,000	1,922,677	1,736,427	1,549,427	2,671,426	1		
6 year, adjusted	77,853,489,832	30,997	0.29	50,000	1,711,182	1,736,427	1,549,427	2,671,426	1		
10 year intervention	137,752,061,064	30,997	0.29	50,000	3,027,724	1,736,427	1,549,427	2,671,426	0		
10 year adjusted	106,069,087,019	30,997	0.29	50,000	2,331,348	1,736,427	1,549,427	2,671,426	1		
	Intervention cost:	Treatment cost	QALY gained	WTP	Number cases						
	LS to all pre-diab	per person	per person	per QALY	To be prevented						
	adjusted:	Base-case (Archimedes)	Base-case (Archimedes)	Most-conservative	to reach CE						
	minus pre-diab to diab				A=C/(T+QW)						

ICER					ICER		
	C	T	Q	W	Observed	Archimedes	Markov
3 year intervention	49,768,658,928	30,997	0.29	50,000	-8,053	***3,875***	-42,644

6 year intervention	87,475,831,272	30,997	0.29	50,000	66,828	***87,793***	6,028
6 year, adjusted	77,853,489,832	30,997	0.29	50,000	47,719	***66,378***	-6,393
10 year intervention	137,752,061,064	30,997	0.29	50,000	166,668	***199,684***	70,924
10 year adjusted	106,069,087,019	30,997	0.29	50,000	103,751	***129,173***	30,028

Incremental Cost-Effectiveness Ratios Calculated for Economic Studies

Prevention of T2DM (for high-risk individuals)														
ID (author+pub year)	Observed or simulated	Intervention	N	Horizon	Perspective	Target pop'n	Country	C	T	RR	Q	TDR	ICER	
DPP-RG 2012	Observed	DPP	3,234	10 years	HCS	IGT and BMI>24	US	3,820	2,197	34%	0.15	0.03	11,000	
Herman 2013	Observed	DPP adhrerers	3,234	10 years	HCS	IGT and BMI>24	US	4,042	4,250	49%	0.13	0.03	20,000	
Irvine	Observed	Norfolk (education, physiotherapy, diet)	177	7 months	HCS	IFG	UK	300	0	NA (Q measured directly)	0.03	0.00	30,000	
Lawlor	Observed except T (based on self-reports of adverse events)	Education	301	2 years	HCS	Pre-diabetes	US	708	2,277				CS	
Sagarra	Observed	Education	552	4 years	HCS	FINDRISC	Spain	125	N/A	37%	0.03	0.00	4,216	
Chen	Observed	Lifestyle		within trial		AUSDRISK1&2	Australia		N/A	30%			cost per case averted around AUS$1000	
Anderson 2012	Simulated	ILC 3 years		Lifetime	Medicare	65+	US	150	5,694		0.29	0.00	CS	high value for T
Anderson with correct T	Simulated	ILC 3 years		Lifetime	Medicare	65+	US	150	3,100		0.29	0.00	4,000	
Eddy 2005 with correct C	Simulated	DPP		Lifetime	HCS	IFG	US	219	3,100		0.29	3.00	27,000	
Gillett	Simulated	DPS		Lifetime	HCS		UK	236		43%	0.07	0.00	2,838	Incidence: 70 to 57 at 20 years
Neumann 2011	Simulated			Lifetime	Societal	30-50	Germany						CS	Societal
Neumann 2011	Simulated			Lifetime	Societal	75+	Germany						30,000	Societal
Palmer 2012	Simulated			Lifetime	HCS		Australia	200	2,145		0.39	5.00	CS	Very generous in cumulative incidence (90 to 73)
Palmer 2012 sensitivity	Simulated			Lifetime	HCS		Australia	200	2,145	DPPOS	0.29	5.00	7,148	
Bertram	Simulated	Diet + exercise		Lifetime	HCS	45+ and pre-diabe	Australia	95	N/A	51%	.05 DAL	3.00	17,250	Cost per DALY
Castro-Rios	Simulated	Screening+Prevention		20 years	HCS	at risk	Mexico		1,200			not provided	CS	Survey data on adverse events and costing
Shaufler 2010	Simulated	DPP		Lifetime	HCS	Pre-diabetes	Germany	715			0.15	5 and 0	728	
Mortaz	Simulated	DPP-style		10 years	HCS	Every 3 years	Canada	575	3,000			0.00	CS	
Screening														
ID (author+pub year)	Observed or simulated	Intervention	N	Horizon	Perspective	Target pop'n	Country	C	T	RR	Q	TDR	ICER	
Khunti	Observed		6,000	1 year			UK						500 to 2000	cost per case detected (two stage: self-reported followed by blo
Schaufler	Simulated			Lifetime			Germany				0.15	5 and 0	CS	
Khan	Simulated	9 strategies		50 years	HCS	at risk	US				0.08	3.00	6,300	screen all 30+ with blood pressure of more than 140/90 every y
Chatterjee	Observed	screening+metf	1,576	3 years	HCS		US		4,174				CS	all strategies are CS

C. NL CPCSSN Data Analysis

CPCSSN Data Analysis Summary Report

Descriptive statistics: Highlights

Background statistics:

- Those with diabetes average approximately 60 years of age, whereas those without diabetes average 43 years of age.
- Males are slightly more likely to be diabetic than females.
- People with diabetes are roughly 2-6 times higher to have diabetes-related medical conditions.
- Diabetes-related clinical indicators have several missing observations for those diagnosed with diabetes. These indicators include body weight, LDL and HDL, SBP/DBP, HbA1c values, FBS values and TC values.

Physician Encounters:

- The mean number of physician encounters is approximately twice as high for those with diabetes than those without diabetes across all years.
- The mean amount of physician encounters has decreased each year since 2009 for those with diabetes, whereas encounter counts have increased each year for those without diabetes.
- The proportion of the total population with diabetes has steadily increased from approximately 5% in 2009 to 10.5% in 2014.
- The number of T2DM-related physician encounters has decreased steadily from an average of 2.4 visits per year in 2009 to 1.6 visits per year in 2014.

Model outputs:

- For those with diabetes, general physician encounters and diabetes-related physician encounters were negatively and significantly associated with age and years 2010 to 2014. Being female is positively and significantly associated with an increase in general physician encounters, and being male is positively and significantly associated with an increase in diabetes-related encounter counts. Interestingly, hypertension and IHD were negatively associated with diabetes-related encounter counts.
- In terms of drugs, years 2011 onwards had significant impacts on the odds of reporting receiving all T2DM-related medications except for metformin. Age appeared to have a strongly significant association with the odds of taking diabetes-related medication, however the magnitudes were small. Being male was negatively and significantly associated with the odds of taking all T2DM medications except sulfonylurea.
- In terms of the total population, having diabetes increased general physician encounter counts three-fold and was highly statistically significant. Males were negatively and significantly associated with physician encounters in the total population. In ascending order (2010-2014), years are positively and significantly associated with encounter

counts, however are negatively and significantly associated when interacted with the presence of diabetes.

Data Request for Economic Modelling

For the economic portion of the project we made a data request for the use of the CPCSSN-APBRN data. We requested data from the CPSSN database to enhance the economic analysis portion of the project in an attempt to speak to the likely economic effectiveness of various diabetes interventions in the NL context.

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) comprises a network of 10 practice-based research across Canada. These networks include family physicians and nurse practitioners who use electronic medical records (EMRs) in their practice. Participants agree to contribute de-identified, point-of-care, patient data form their practices, on a quarterly basis, to the CPCSSN database.

The Atlantic Practice Based Research Network (APBRN) is Newfoundland and Labrador's network of primary care providers lead by Director, Dr. Marshall Godwin (www.med.mun.ca/phru/apbrn.aspx). According to the CPCSSN website, 117 physicians and nurses from the Province are a part of APBRN.

We requested the following variables for our analysis:

Table 20: Data variables requested from CPCSSN-NL

Data Grouping	Variables	Description	Rationale	Years Requested
CPCSSN Patient Demographics for all NL adults 18 years or older	Patient ID	ID Assigned by CPCSSN	Index variable: to identify discrete cases.	2009-2014
	Sex.	Male or Female	Grouping and gender comparisons	2009-2014
	Birth Year	Four digit year	Grouping and age comparisons.	2009-2014
	Post Code for adults 18 yrs or older.	6 character code	Regional groupings and identification comparisons of regional effects.	2009-2014
	Deceased year	Four digit year	Dependent variable/outcome that relates directly to the research question.	2009-2014
Provider Information	Provider ID	ID assigned by CPCSSN	Index variable: to help us identify provider cases of T2D.	2009-2014
Encounter Data	# of encounters (any diagnosis) per year		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	# of encounters for Diabetes per year		To provide data for economic modelling of	For each year: 2009, 2010, 2011,

			T2D clinical or cost effectiveness for NL	2012, 2013, 2014
Lab Data	# hemoglobin A1C tests ordered for the patient per year		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	Average hemoglobin A1C value for the patient per year.		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	# of fasting blood sugar tests ordered for the patient per year		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	Average fasting blood sugar value for the patient per year.		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	# of Lipid profiles ordered for the patient per year		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	Average total cholesterol value for the patient per year.		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	Average LDL value for the patient per year.		To provide data for economic modelling of T2D clinical or cost effectiveness for NL.	For each year: 2009, 2010, 2011, 2012, 2013, 2014
	Average HDL value for the patient per year.		To provide data for economic modelling of T2D clinical or cost effectiveness for NL	For each year: 2009, 2010, 2011, 2012, 2013, 2014
Medical Conditions	Diabetes	Presence of diabetes based on CPCSSN algorithm Y or N	Dependent variable: speaks to patient health.	If present in 2009 assume present all subsequent years. If not present 2009 indicate which year occurs and then Yes all

				subsequent years
	Hypertension	Presence of hypertension based on CPCSSN algorithm Y or N	Dependent variable/co-variable: speaks to comorbid conditions.	If present in 2009 assume present all subsequent years. If not present 2009 indicate which year occurs and then Yes all subsequent years
	Hyperlipidemia	Presence of hyperlipidemia Y or N	Dependent variable/co-variable: speaks to comorbid conditions.	If present in 2009 assume present all subsequent years. If not present 2009 indicate which year occurs and then Yes all subsequent years 2014
	Ischemic Heart Disease	Presence of Ischemic Heart Disease Y or N	Dependent variable/co-variable: speaks to comorbid conditions.	If present in 2009 assume present all subsequent years. If not present 2009 indicate which year occurs and then Yes all subsequent years
	Cerebrovascular Disease	Presence of Cerebrovascular Disease Y or N	Dependent variable/co-variable: speaks to comorbid conditions.	If present in 2009 assume present all subsequent years. If not present 2009 indicate which year occurs and then Yes all subsequent years

Physical Exam Table	Average blood pressure (systolic and diastolic) results each year	Co-variable: risk factor for diabetes.	For each year: 2009, 2010, 2011, 2012, 2013, 2014

Description of data received

Overall the dataset includes over 200,000 observations, and about 36000 unique observations (meaning individuals). A graduate student working under the supervision of the health economist for the project analyzed the data

In models where we excluded covariates with missing data, the sample size is 36,614. There are only a couple with that number. The rest of the models, which were only run with individuals with low or no missing data, range from about 850 to 7500. The smaller numbers of 'groups' or patients in the regressions exist in models conditional on having diabetes (so they are the only population included).

Below is the variable key for the dataset we received. These variables were used to formulate descriptive statistics and modelling outputs.

Variable Key		
	Variables	Description
Demographic	Age	Continuous
	Sex	Male=1, Female=0
Medical Conditions	Diabetes	Presence or absence of condition(binary with presence=1)
	Hypertension	
	Hyperlipidemia	
	IHD	
	Cerebrovascular Disease	
Clinical Indicators	Bodyweight	Continuous
	LDL Value	Continuous
	HDL Value	Continuous
	Systolic BP	Continuous

	Diastolic BP	Continuous
Medications	Insulin	Presence or absence of medication (binary with presence=1)
	Metformin	
	Sulfonylurea	
	Other Oral Hypoglycemic	
Year Indicators	yr09-yr14	Dummy variables for dataset year. yr09 (2009) is the reference.
	Diabetes09-14	Interaction variables between diabetes and year. Diabetes09 (2009) is the reference.

Diabetes-related clinical indicators have several missing observations for those diagnosed with diabetes. These indicators include body weight, LDL and HDL, SBP/DBP, HbA1c values, FBS values and TC values. Covariates with missing observations are listed in the table below.

Table 21: Table of covariates with missing observations

*Table of covariates with missing observations		
Covariates	Included	Missing
Body Weight	3347	13613
LDL	7483	9477
HDL	7612	9348
SBP	10394	6566
DBP	10392	6568
HbA1c Value	7788	9172
FBS Value	7137	9823
TC Value	7616	9344

Descriptive Statistics

Descriptive Statistics by Diabetes Diagnosis

Overall descriptive statistics include the number of observations, mean, standard deviation, and quartiles-25, 50 and 75th for each variable and the demographic, medical conditions, clinical indicators, medications and years for those with and without diabetes.

Table 22: Summary of descriptive statistics

Descriptive Statistics by Diabetes Diagnosis																		
	Presence or Absence of Diabetes																	
	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
	Number (n)			Mean			SD			p25			p50			p75		
Demographics																		
Age	16960	196062	213022	59.663	43.343	44.643	15.239	17.743	18.104	51.000	29.000	30.000	61.000	42.000	43.000	70.000	56.000	58.000
Sex (Proportion male)	16960	196056	213016	0.486	0.401	0.408	0.5	0.49	0.491	0.000	0.000	0.000	0.000	0.000	0.000	1.000	1.000	1.000
Utilization																		
Total Physician Encounters	16960	196062	213022	5.778	2.828	3.063	4.966	3.919	4.091	2.000	0.000	0.000	5.000	1.000	2.000	8.000	4.000	5.000
T2DM Encounters	16960	196062	213022	1.745	0.012	0.15	2.036	0.161	0.757	0.000	0.000	0.000	1.000	0.000	0.000	3.000	0.000	0.000
Medical Conditions																		
Hypertension	16960	196062	213022	0.47	0.137	0.164	0.499	0.344	0.37	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000
Hyperlipidemia	16960	196062	213022	0.59	0.164	0.198	0.492	0.37	0.398	0.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000
IHD	16960	196062	213022	0.182	0.033	0.045	0.386	0.178	0.206	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CD	16960	196062	213022	0.024	0.005	0.006	0.152	0.07	0.08	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Clinical Indicators																		
Body Weight	3347	16777	20124	94.862	82.392	84.466	26.692	24.125	25.004	76.200	66.033	67.300	91.500	78.422	80.300	107.950	94.167	96.700
LDL	7483	32823	40306	2.373	3.122	2.983	0.847	0.88	0.921	1.780	2.500	2.300	2.200	3.100	2.930	2.850	3.700	3.600
HDL	7612	33076	40688	1.119	1.312	1.276	0.299	0.359	0.357	0.920	1.060	1.020	1.070	1.260	1.220	1.270	1.510	1.470
SBP	10394	59787	70181	128.379	123.445	124.175	12.7	13.749	13.711	120.000	114.000	115.000	128.000	122.667	124.000	136.000	132.000	132.500
DBP	10392	59765	70157	74.752	75.37	75.279	7.994	8.618	8.531	70.000	70.000	70.000	74.667	75.500	75.176	80.000	80.500	80.000
HbA1c Count	16960	196062	213022	1.089	0.055	0.137	1.774	0.349	0.664	0.000	0.000	0.000	0.000	0.000	0.000	2.000	0.000	0.000
HbA1c Value	7788	6986	14774	7.453	5.722	6.634	1.406	0.421	1.368	6.500	5.400	5.700	7.200	5.700	6.200	8.100	6.000	7.250
FBS Count	16960	196062	213022	0.975	0.280	0.336	1.695	0.902	1.006	0.000	0.000	0.000	0.000	0.000	0.000	2.000	0.000	0.000
FBS Value	7137	32243	39380	8.218	5.307	5.835	2.772	0.585	1.712	6.470	4.900	5.000	7.570	5.300	5.400	9.180	5.600	6.000
Lipid Count	16960	196062	213022	4.009	1.220	1.442	6.611	3.873	4.225	0.000	0.000	0.000	0.000	0.000	0.000	8.000	0.000	0.000
TC Value	7616	33045	40661	4.313	5.101	4.953	1.044	1.032	1.079	3.580	4.400	4.200	4.160	5.060	4.900	4.900	5.770	5.660
Medications																		
Insulin	16960	196062	213022	0.143	0.000	0.011	0.350	0.000	0.106	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Metformin	16960	196062	213022	0.416	0.000	0.033	0.493	0.011	0.179	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000
Sulfonylurea	16960	196062	213022	0.187	0.000	0.015	0.390	0.000	0.121	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Other Hypoglycemic	16960	196062	213022	0.060	0.000	0.005	0.237	0.008	0.069	0.000	0.000	0	0.000	0.000	0	0.000	0.000	0.000
Year																		
2009	16960	196062	213022	0.103	0.166	0.161	0.303	0.372	0.368	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2010	16960	196062	213022	0.127	0.167	0.164	0.333	0.373	0.37	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2011	16960	196062	213022	0.158	0.166	0.166	0.365	0.372	0.372	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2012	16960	196062	213022	0.18	0.167	0.168	0.384	0.373	0.374	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2013	16960	196062	213022	0.206	0.167	0.17	0.404	0.373	0.376	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2014	16960	196062	213022	0.227	0.167	0.172	0.419	0.373	0.377	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Physician Encounters

Table 22 shows descriptive statistics representing the number, mean, standard deviation and quartiles of those with diabetes within the total population and physician encounter counts for the total population, by year.

Table 23: Physician encounters and T2D in the total population by year and overall

Proportion of the Population with Diabetes and Number of Physician Encounters (Total Population)							
YEAR		**Number**	**Mean**	**Standard Deviation**	**p25**	**p50**	**p75**
2009	Presence of Diabetes (Proportion)	34295	**0.051**	0.219	0.000	0.000	0.000
	Encounter Count	34295	**2.596**	3.853	0.000	1.000	4.000
2010	Presence of Diabetes (Proportion)	34841	**0.062**	0.241	0.000	0.000	0.000
	Encounter Count	34841	**2.806**	4.053	0.000	1.000	4.000
2011	Presence of Diabetes (Proportion)	35302	**0.076**	0.265	0.000	0.000	0.000
	Encounter Count	35302	**3.140**	4.124	0.000	2.000	5.000
2012	Presence of Diabetes (Proportion)	35781	**0.085**	0.279	0.000	0.000	0.000
	Encounter Count	35781	**3.261**	4.136	0.000	2.000	5.000
2013	Presence of Diabetes (Proportion)	36188	**0.096**	0.295	0.000	0.000	0.000
	Encounter Count	36188	**3.236**	4.138	0.000	2.000	5.000
2014	Presence of Diabetes (Proportion)	36615	**0.105**	0.307	0.000	0.000	0.000
	Encounter Count	36615	**3.306**	4.173	0.000	2.000	5.000
Total	Presence of Diabetes (Proportion)	213022	**0.080**	0.271	0.000	0.000	0.000
	Encounter Count	213022	**3.063**	4.091	0.000	2.000	5.000

Table 23 shows the number, mean, standard deviation and quartiles of type 2 diabetes-related physician encounters for individuals diagnosed with T2D arranged by year.

Table 24: Number of T2DM related physician encounters for those with T2D, by year

Number of T2D Related Physician Encounters For those Diagnosed with T2D, by Year						
Year	**Number(n)**	**Mean**	**Standard Deviation**	**p25**	**p50**	**p75**
2009	1740	2.357	2.437	0.000	2.000	3.000
2010	2156	1.937	2.174	0.000	1.000	3.000
2011	2676	1.74	1.981	0.000	1.000	3.000
2012	3056	1.616	1.914	0.000	1.000	3.000
2013	3487	1.557	1.891	0.000	1.000	3.000
2014	3845	1.636	1.953	0.000	1.000	3.000
Total	16960	1.745	2.036	0.000	1.000	3.000

Table 24 shows descriptive statistics of the number, mean, standard deviation, and quartiles of total physician encounter counts by year for those with and without diabetes. Columns highlighted in pale orange show numbers pertaining to those diagnosed with T2D.

Table 25: Physician encounter count for those with and without diabetes, by year

Physician Encounter Count for those with and without Diabetes, by Year												
Year	Number		Mean		Standard Deviation		p25		p50		p75	
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
2009	1740	32555	6.491	2.387	4.983	3.668	3.000	0.000	6.000	1.000	9.000	4.000
2010	2156	32685	6.267	2.577	4.971	3.878	3.000	0.000	5.000	1.000	9.000	4.000
2011	2676	32626	5.968	2.908	5.054	3.949	2.000	0.000	5.000	1.000	8.000	4.000
2012	3056	32725	5.784	3.025	4.959	3.970	2.000	0.000	5.000	2.000	8.000	5.000
2013	3487	32701	5.484	2.996	4.899	3.975	2.000	0.000	5.000	2.000	8.000	5.000
2014	3845	32770	5.313	3.070	4.892	4.015	2.000	0.000	5.000	2.000	8.000	5.000
Total	16960	196062	5.778	2.828	4.966	3.919	2.000	0.000	5.000	1.000	8.000	4.000

Demographic Characteristics

Table 25 presents a tabulation of the number and percentage of demographic characteristics, medical conditions and medication usage for those with and without a diagnosis of T2D.

Table 26: Demographic characteristics, medical conditions and medication usage for those with and without T2D

Tabulations of Demographics, Medical Conditions and Pharmacotherapy by Presence of Diabetes						
	Presence of Diabetes					
	Yes		No			
	Percentage	Number(n)	Percentage	Number(n)	Pearson chi2(df)	p
Demographics						
Male	48.59	8,241	40.10	78,621	465.856(1)	0.000
Female	51.41	8,719	59.90	117,435	465.856(1)	0.000
Medical Conditions						
Hypertension	46.96	7,964	13.70	26,868	1.3e+04(1)	0.000
Hyperlipidemia	58.95	9,998	16.37	32,100	1.8e+04(1)	0.000
IHD	18.23	3091	3.27	6402	8200(1)	0.000
Cerebrovascular Disease	2.38	403	0.49	961	872.7523(1)	0.000
Pharmacotherapy						
Insulin	14.30	2425	N/A	NA/	28000(1)	0.000
Metformin	41.58	7052	N/A	NA/	84000(1)	0.000
Sulfonylurea	18.74	3178	N/A	NA/	37000(1)	0.000
Other Oral Hypoglycemic	5.99	1016	N/A	NA/	12000(1)	0.000

T2D Medications and Related Medications

Table 26 presents, by year, the number, mean, standard deviation and quartiles of the total population (with and without T2DM) who report using T2DM-related medications.

Table 27: Proportion of the population with T2D using T2D treatments

Proportion of Total Population Using T2D Treatments							
YEAR		Number(n)	Mean	Standard Deviation	p25	p50	p75
2009	Insulin	34295	0.70%	0.084	0.000	0.000	0.000
	Metformin	34295	2.40%	0.154	0.000	0.000	0.000
	Sulfonylurea	34295	1.20%	0.111	0.000	0.000	0.000
	Other Oral Hypoglycemic	34295	0.40%	0.063	0.000	0.000	0.000
2010	Insulin	34841	0.90%	0.095	0.000	0.000	0.000
	Metformin	34841	2.80%	0.165	0.000	0.000	0.000
	Sulfonylurea	34841	1.30%	0.114	0.000	0.000	0.000
	Other Oral Hypoglycemic	34841	0.40%	0.067	0.000	0.000	0.000
2011	Insulin	35302	1.10%	0.106	0.000	0.000	0.000
	Metformin	35302	3.40%	0.182	0.000	0.000	0.000
	Sulfonylurea	35302	1.60%	0.125	0.000	0.000	0.000
	Other Oral Hypoglycemic	35302	0.50%	0.069	0.000	0.000	0.000
2012	Insulin	35781	1.30%	0.112	0.000	0.000	0.000
	Metformin	35781	3.60%	0.187	0.000	0.000	0.000
	Sulfonylurea	35781	1.60%	0.125	0.000	0.000	0.000
	Other Oral Hypoglycemic	35781	0.50%	0.068	0.000	0.000	0.000
2013	Insulin	36188	1.30%	0.115	0.000	0.000	0.000
	Metformin	36188	3.70%	0.190	0.000	0.000	0.000
	Sulfonylurea	36188	1.60%	0.126	0.000	0.000	0.000
	Other Oral Hypoglycemic	36188	0.50%	0.073	0.000	0.000	0.000
2014	Insulin	36615	1.40%	0.119	0.000	0.000	0.000
	Metformin	36615	3.80%	0.192	0.000	0.000	0.000
	Sulfonylurea	36615	1.60%	0.125	0.000	0.000	0.000
	Other Oral Hypoglycemic	36615	0.60%	0.075	0.000	0.000	0.000
Total	Insulin	213022	1.10%	0.106	0.000	0.000	0.000
	Metformin	213022	3.30%	0.179	0.000	0.000	0.000
	Sulfonylurea	213022	1.50%	0.121	0.000	0.000	0.000
	Other Oral Hypoglycemic	213022	0.50%	0.069	0.000	0.000	0.000

Table 27 reports the same figures for the population reporting a T2D diagnosis only.

Table 28: Proportion of the diabetic population using T2D treatments

Proportion of Diabetic Population Using T2D Treatments							
YEAR		Number (n)	Mean	Standard Deviation	p25	p50	p75
2009	Insulin	1740	14.10%	0.349	0.000	0.000	0.000
	Metformin	1740	47.80%	0.500	0.000	0.000	1.000
	Sulfonylurea	1740	24.60%	0.431	0.000	0.000	0.000
	Other Oral Hypoglycemic	1740	7.60%	0.265	0.000	0.000	0.000
2010	Insulin	2156	14.70%	0.354	0.000	0.000	0.000
	Metformin	2156	45.20%	0.498	0.000	0.000	1.000
	Sulfonylurea	2156	21.20%	0.408	0.000	0.000	0.000
	Other Oral Hypoglycemic	2156	7.20%	0.258	0.000	0.000	0.000
2011	Insulin	2676	15.00%	0.357	0.000	0.000	0.000
	Metformin	2676	45.00%	0.498	0.000	0.000	1.000
	Sulfonylurea	2676	20.80%	0.406	0.000	0.000	0.000
	Other Oral Hypoglycemic	2676	6.30%	0.243	0.000	0.000	0.000
2012	Insulin	3056	14.80%	0.355	0.000	0.000	0.000
	Metformin	3056	42.30%	0.494	0.000	0.000	1.000
	Sulfonylurea	3056	18.70%	0.390	0.000	0.000	0.000
	Other Oral Hypoglycemic	3056	5.30%	0.225	0.000	0.000	0.000
2013	Insulin	3487	13.90%	0.346	0.000	0.000	0.000
	Metformin	3487	38.80%	0.487	0.000	0.000	1.000
	Sulfonylurea	3487	16.70%	0.373	0.000	0.000	0.000
	Other Oral Hypoglycemic	3487	5.50%	0.228	0.000	0.000	0.000
2014	Insulin	3845	13.60%	0.343	0.000	0.000	0.000
	Metformin	3845	36.30%	0.481	0.000	0.000	1.000
	Sulfonylurea	3845	15.20%	0.359	0.000	0.000	0.000
	Other Oral Hypoglycemic	3845	5.40%	0.225	0.000	0.000	0.000
Total	Insulin	16960	14.30%	0.350	0.000	0.000	0.000
	Metformin	16960	41.60%	0.493	0.000	0.000	1.000
	Sulfonylurea	16960	18.70%	0.390	0.000	0.000	0.000
	Other Oral Hypoglycemic	16960	6.00%	0.237	0.000	0.000	0.000

Select Medical Conditions

Table 28 presents, by year, the number, mean, standard deviation and quartiles of the total population (with and without T2D) who report having diabetes and T2D-related medical conditions. The percentage of those reporting having diabetes are highlighted in orange.

Table 29: Prevalence of select medical conditions within total population, by year

Prevalence of Select Medical Conditions within Total Population, by Year							
YEAR		Number(n)	Mean	Standard Deviation	p25	p50	p75
2009	Diabetes	34295	**5.100%**	0.219	0.000	0.000	0.000
	Hypertension	34295	**11.100%**	0.314	0.000	0.000	0.000
	Hyperlipidemia	34295	**13.200%**	0.338	0.000	0.000	0.000
	IHD	34295	**3.000%**	0.171	0.000	0.000	0.000
	Cerebrovascular Disease	34295	**0.400%**	0.065	0.000	0.000	0.000
2010	Diabetes	34841	**6.200%**	0.241	0.000	0.000	0.000
	Hypertension	34841	**13.300%**	0.339	0.000	0.000	0.000
	Hyperlipidemia	34841	**15.800%**	0.364	0.000	0.000	0.000
	IHD	34841	**3.500%**	0.185	0.000	0.000	0.000
	Cerebrovascular Disease	34841	**0.500%**	0.070	0.000	0.000	0.000
2011	Diabetes	35302	**7.600%**	0.265	0.000	0.000	0.000
	Hypertension	35302	**15.700%**	0.363	0.000	0.000	0.000
	Hyperlipidemia	35302	**19.000%**	0.393	0.000	0.000	0.000
	IHD	35302	**4.200%**	0.202	0.000	0.000	0.000
	Cerebrovascular Disease	35302	**0.600%**	0.076	0.000	0.000	0.000
2012	Diabetes	35781	**8.500%**	0.279	0.000	0.000	0.000
	Hypertension	35781	**17.300%**	0.378	0.000	0.000	0.000
	Hyperlipidemia	35781	**21.500%**	0.411	0.000	0.000	0.000
	IHD	35781	**4.700%**	0.212	0.000	0.000	0.000
	Cerebrovascular Disease	35781	**0.700%**	0.082	0.000	0.000	0.000
2013	Diabetes	36188	**9.600%**	0.295	0.000	0.000	0.000
	Hypertension	36188	**19.100%**	0.393	0.000	0.000	0.000
	Hyperlipidemia	36188	**23.300%**	0.423	0.000	0.000	0.000
	IHD	36188	**5.200%**	0.223	0.000	0.000	0.000
	Cerebrovascular Disease	36188	**0.800%**	0.087	0.000	0.000	0.000
2014	Diabetes	36615	**10.500%**	0.307	0.000	0.000	0.000
	Hypertension	36615	**21.200%**	0.409	0.000	0.000	0.000
	Hyperlipidemia	36615	**25.200%**	0.434	0.000	0.000	1.000
	IHD	36615	**5.900%**	0.235	0.000	0.000	0.000
	Cerebrovascular Disease	36615	**0.900%**	0.093	0.000	0.000	0.000
Total	Diabetes	213022	**8.000%**	0.271	0.000	0.000	0.000
	Hypertension	213022	**16.400%**	0.370	0.000	0.000	0.000
	Hyperlipidemia	213022	**19.800%**	0.398	0.000	0.000	0.000
	IHD	213022	**4.500%**	0.206	0.000	0.000	0.000
	Cerebrovascular Disease	213022	**0.600%**	0.080	0.000	0.000	0.000

Table 29 reports the same figures for the population reporting those with T2D diagnosis only.

Table 30: Prevalence of select comorbidities within diabetic population, by year

Prevalence of Select Comorbidities within Diabetic Population, by Year							
YEAR		**Number(n)**	**Mean**	**Standard Deviation**	**p25**	**p50**	**p75**
2009	Hypertension	1740	0.397	0.489	0.000	0.000	1.000
	Hyperlipidemia	1740	0.525	0.500	0.000	1.000	1.000
	IHD	1740	0.174	0.379	0.000	0.000	0.000
	Cerebrovascular Disease	1740	0.024	0.154	0.000	0.000	0.000
2010	Hypertension	2156	0.429	0.495	0.000	0.000	1.000
	Hyperlipidemia	2156	0.568	0.495	0.000	1.000	1.000
	IHD	2156	0.176	0.381	0.000	0.000	0.000
	Cerebrovascular Disease	2156	0.022	0.148	0.000	0.000	0.000
2011	Hypertension	2676	0.437	0.496	0.000	0.000	1.000
	Hyperlipidemia	2676	0.576	0.494	0.000	1.000	1.000
	IHD	2676	0.178	0.383	0.000	0.000	0.000
	Cerebrovascular Disease	2676	0.022	0.147	0.000	0.000	0.000
2012	Hypertension	3056	0.461	0.499	0.000	0.000	1.000
	Hyperlipidemia	3056	0.599	0.490	0.000	1.000	1.000
	IHD	3056	0.182	0.386	0.000	0.000	0.000
	Cerebrovascular Disease	3056	0.023	0.150	0.000	0.000	0.000
2013	Hypertension	3487	0.487	0.500	0.000	0.000	1.000
	Hyperlipidemia	3487	0.604	0.489	0.000	1.000	1.000
	IHD	3487	0.183	0.387	0.000	0.000	0.000
	Cerebrovascular Disease	3487	0.025	0.155	0.000	0.000	0.000
2014	Hypertension	3845	0.539	0.499	0.000	1.000	1.000
	Hyperlipidemia	3845	0.620	0.486	0.000	1.000	1.000
	IHD	3845	0.192	0.394	0.000	0.000	0.000
	Cerebrovascular Disease	3845	0.025	0.158	0.000	0.000	0.000
Total	Hypertension	16960	0.470	0.499	0.000	0.000	1.000
	Hyperlipidemia	16960	0.590	0.492	0.000	1.000	1.000
	IHD	16960	0.182	0.386	0.000	0.000	0.000
	Cerebrovascular Disease	16960	0.024	0.152	0.000	0.000	0.000

Model Outputs

Encounter Models for those with diabetes

Encounter Model #1 - Diabetic Population

Table 31: Physician encounter count for those with diabetes, regression results (Model # 1 Diabetic Population)

Physican Encounter Count for those with Diabetes- Regression Results							
Group Variance: Patient_id				Number of Obs	1545		
				Number of Groups	849		
R-squared within	0.0214		Obs per group	Min	1		
R-squared between	0.0613			Avg	1.8		
R-squared overall	0.0537			Max	6		
			Wald chi2(20)	63.95	prob>chi2= 0.0000		
		(Std. Err. adjusted for 849 clusters in patient_id)					
encounter_count	Coef.	Robust Standard Error	z	P>z	[95% Conf.	Interval]	
age	-0.0125064	0.0147089	-0.85	0.395	-0.0413353	0.0163226	
male	-0.4950843	0.3166422	-1.56	0.118	-1.115692	0.125523	
hba1c_value	0.3193953	0.1256663	2.54	0.011	0.0730939	0.5656968	
fbs_value	-0.0178892	0.0609938	-0.29	0.769	-0.1374348	0.1016564	
lipid_count	0.079398	0.0180637	4.4	0	0.0439939	0.1148022	
tc_value	0.3371083	0.3699909	0.91	0.362	-0.3880605	1.062277	
hypertension	0.506224	0.2842392	1.78	0.075	-0.0508745	1.063322	
hyperlipidemia	0.4075671	0.2930288	1.39	0.164	-0.1667588	0.981893	
ihd	0.87353	0.3606768	2.42	0.015	0.1666166	1.580444	
cerebrovascular_disease	0.7644394	1.255425	0.61	0.543	-1.696149	3.225028	
bodyweight	0.001499	0.0057047	0.26	0.793	-0.0096821	0.01268	
ldl_value	-0.4437103	0.410857	-1.08	0.28	-1.248975	0.3615547	
hdl_value	-0.1293461	0.6074605	-0.21	0.831	-1.319947	1.061255	
sbp	-0.0061414	0.0117851	-0.52	0.602	-0.0292397	0.016957	
dbp	0.0020117	0.0181275	0.11	0.912	-0.0335176	0.037541	
yr10	-0.0807413	0.3175389	-0.25	0.799	-0.7031062	0.5416235	
yr11	-0.2652732	0.4112156	-0.65	0.519	-1.071241	0.5406946	
yr12	-0.4565678	0.364513	-1.25	0.21	-1.171	0.2578647	
yr13	-0.728746	0.3513998	-2.07	0.038	-1.417477	-0.040015	
yr14	-1.037288	0.3450325	-3.01	0.003	-1.713539	-0.361037	
_cons	5.977397	2.212101	2.7	0.007	1.641758	10.31304	
sigma_u	3.2956674						
sigma_e	3.0591276						
rho	0.53717076	(fraction of variance due to u_i)					

Encounter Model #2 – Diabetic Population

Table 32: Physician encounter count for those with diabetes, regression results (Model #2 Diabetic Population)

Diabetes-Related Physican Encounter Count for those with Diabetes- Regression Results						
Group Variance: Patient_id				Number of Obs	1545	
				Number of Groups	849	
R-squared within	0.0837		Obs per group	Min	1	
R-squared between	0.2409			Avg	1.8	
R-squared overall	0.214			Max	6	
			Wald chi2(20)	258.93	prob>chi2= 0.0000	
			(Std. Err. adjusted for 849 clusters in patient_id)			
dm_encounter_ count	Coef.	Robust Std. Err.	z	P>z	[95% Conf.Interval]	
age	-0.0129532	0.0057841	-2.24	0.025	-0.0242898	-0.0016166
male	0.5218753	0.1324447	3.94	0	0.2622885	0.7814621
hba1c_value	0.5625818	0.0591311	9.51	0	0.446687	0.6784766
fbs_value	0.01238	0.0347971	0.36	0.722	-0.0558211	0.0805811
lipid_count	0.0486526	0.0077796	6.25	0	0.0334049	0.0639003
tc_value	0.0675111	0.1606732	0.42	0.674	-0.2474025	0.3824248
hypertension	-0.2358048	0.1260282	-1.87	0.061	-0.4828155	0.011206
hyperlipidemia	0.0349751	0.1349435	0.26	0.795	-0.2295093	0.2994595
ihd	-0.2462202	0.1641056	-1.5	0.134	-0.5678613	0.0754208
cerebrovascular _disease	0.4394988	0.3862262	1.14	0.255	-0.3174907	1.196488
bodyweight	-0.0078077	0.0023472	-3.33	0.001	-0.0124081	-0.0032073
ldl_value	-0.1830968	0.1772325	-1.03	0.302	-0.5304661	0.1642724
hdl_value	-0.4364546	0.2228701	-1.96	0.05	-0.873272	0.0003627
sbp	-0.0056294	0.0056765	-0.99	0.321	-0.0167552	0.0054964
dbp	-0.0036188	0.0087808	-0.41	0.68	-0.0208289	0.0135913
yr10	-0.2947893	0.1572692	-1.87	0.061	-0.6030313	0.0134526
yr11	-0.6075255	0.1869211	-3.25	0.001	-0.9738841	-0.2411668
yr12	-0.4281986	0.1728356	-2.48	0.013	-0.7669501	-0.0894471
yr13	-0.6272035	0.1762534	-3.56	0	-0.9726539	-0.2817532
yr14	-0.4318858	0.1699424	-2.54	0.011	-0.7649667	-0.0988049
_cons	1.503934	0.9234652	1.63	0.103	-0.3060245	3.313893
sigma_u	1.1355158					
sigma_e	1.6189629					
rho	0.329732	(fraction	of	variance	due	to u_i)

Encounter Model #3 Diabetic Population

Table 33: Physician encounter count for those with diabetes, regression results (Model #3 Diabetic Population)

Physican Encounter Count for those with Diabetes- Regression Results						
Group Variance: Patient_id				Number of Obs	16960	
				Number of Groups	3845	
R-squared within	0.0503		Obs per group	Min	1	
R-squared between	0.0833			Avg	4.4	
R-squared overall	0.0845			Max	6	
			Wald chi2(12)	525.07	prob>chi2= 0.0000	
		(Std. Err. adjusted for 3845 clusters in patient_id)				
		Robust				
encounter_count	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
age	-0.0216793	0.0045565	-4.76	0.000	-0.0306099	-0.0127487
male	-0.8477409	0.1262049	-6.72	0.000	-1.095098	-0.6003838
lipid_count	0.1078224	0.01867	5.78	0.000	0.0712298	0.144415
hypertension	0.6301041	0.1151795	5.47	0.000	0.4043565	0.8558518
hyperlipidemia	1.09237	0.1196772	9.13	0.000	0.8578071	1.326933
ihd	0.820965	0.1637767	5.01	0.000	0.4999685	1.141962
cerebrovascular_disease	0.5542999	0.3891726	1.42	0.154	-0.2084644	1.317064
yr10	-0.160488	0.101259	-1.58	0.113	-0.3589521	0.037976
yr11	-0.3112426	0.1249676	-2.49	0.013	-0.5561746	-0.0663105
yr12	-0.7317792	0.1167995	-6.27	0.000	-0.9607021	-0.5028564
yr13	-1.179662	0.118018	-10	0.000	-1.410973	-0.9483505
yr14	-1.448417	0.121225	-11.95	0.000	-1.686013	-1.21082
_cons	6.82482	0.3136407	21.76	0.000	6.210095	7.439545
sigma_u	3.4629349					
sigma_e	3.0962274					
rho	0.55573346	(fraction	of variance due	to	u_i)	

Encounter Model #4 Diabetic Population

Table 34: Physician encounter count for those with diabetes, regression results (Model #4 Diabetic Population)

Diabetes-Related Physican Encounter Count for those with Diabetes- Regression Results						
Group Variance: Patient_id				Number of Obs	1545	
				Number of Groups	849	
R-squared within	0.0585		Obs per group	Min	1	
R-squared between	0.0754			Avg	1.8	
R-squared overall	0.0807			Max	6	
			Wald chi2(12)	519.3	prob>chi2= 0.0000	
		(Std. Err. adjusted for 3845 clusters in patient_id)				
dm_encounter_count	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
age	-0.0097861	0.0015571	-6.28	0.000	-0.0128381	-0.0067342
male	0.192997	0.0479893	4.02	0.000	0.0989397	0.2870543
lipid_count	0.0538096	0.0075535	7.12	0.000	0.039005	0.0686143
hypertension	-0.0751534	0.0478786	-1.57	0.116	-0.1689937	0.018687
hyperlipidemia	0.4894286	0.0503762	9.72	0.000	0.3906931	0.5881642
ihd	-0.1566723	0.0609637	-2.57	0.01	-0.276159	-0.0371856
cerebrovascular_disease	0.0362587	0.1779297	0.2	0.839	-0.3124772	0.3849945
yr10	-0.3367601	0.0548775	-6.14	0.000	-0.4443179	-0.2292022
yr11	-0.4565897	0.0614581	-7.43	0.000	-0.5770453	-0.3361341
yr12	-0.6680841	0.0588744	-11.35	0.000	-0.7834758	-0.5526923
yr13	-0.7642707	0.0592166	-12.91	0.000	-0.880333	-0.6482083
yr14	-0.6862219	0.0595019	-11.53	0.000	-0.8028435	-0.5696003
_cons	2.356481	0.1138024	20.71	0.000	2.133433	2.57953
sigma_u	1.2054302					
sigma_e	1.4868197					
rho	0.39661109	(fraction	of variance due	to	u_i)	

Encounter Models Total Population

Encounter Model #1 – Total Population

Table 35: Physician encounter count, total population, regression results excluding covariates with missing observations (Encounter Model #1 Total Population)

Physician encounter count for total population- regression results: Excluding covariates with missing observations

Random-effects GLS regression			Number of obs =	213016		
Group variable: patient_id			Number of groups =	36614		
R-sq: within = 0.0548			Obs per group: min =	1		
between = 0.1782			avg =	5.8		
overall = 0.1318			max =	6		
			Wald chi2(17) =	9592.73		
corr(u_i, X) = 0 (assumed)			Prob > chi2 =	0.0000		
			(Std. Err. adjusted for 36614 clusters in patient_id)			
		Robust				
encounter_count	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
diabetes	3.009311	0.1084981	27.74	0	2.796658	3.221963
age	-0.0010566	0.0009231	-1.14	0.252	-0.0028658	0.0007525
male	-1.034481	0.0297026	-34.83	0	-1.092697	-0.976265
hypertension	1.854831	0.0480245	38.62	0	1.760705	1.948957
hyperlipidemia	1.770954	0.0413605	42.82	0	1.689889	1.852019
ihd	1.231448	0.0872427	14.12	0	1.060456	1.402441
cerebrovascular_diseas	0.8574661	0.2294537	3.74	0	0.4077453	1.307187
yr10	0.1193401	0.0168277	7.09	0	0.0863585	0.1523218
yr11	0.3562176	0.020489	17.39	0	0.3160598	0.3963753
yr12	0.4112937	0.0223361	18.41	0	0.3675158	0.4550717
yr13	0.3295718	0.0234299	14.07	0	0.2836502	0.3754935
yr14	0.3472723	0.0245245	14.16	0	0.2992052	0.3953394
diabetes10	-0.5241805	0.1020875	-5.13	0	-0.7242683	-0.3240927
diabetes11	-1.146141	0.1117827	-10.25	0	-1.365231	-0.9270507
diabetes12	-1.544945	0.1138458	-13.57	0	-1.768079	-1.321811
diabetes13	-1.88183	0.1138625	-16.53	0	-2.104997	-1.658664
diabetes14	-2.249562	0.1150576	-19.55	0	-2.47507	-2.024053
_cons	2.428904	0.0436556	55.64	0	2.34334	2.514467
sigma_u	2.6517676					
sigma_e	2.7214586					
rho	0.48703212	(fraction	of variance d	to	u_i)	

Encounter Model #2 – Total Population

Table 36: Physician encounter count for total population, regression results including all covariates (Encounter Model #2 Total Population)

Physician encounter count for total population- regression results: Including all covariates

Random-effects GLS regression			Number of obs =	7729		
Group variable: patient_id			Number of groups =	4574		
R-sq: within = 0.0051			Obs per group: min =	1		
between = 0.0793			avg =	1.7		
overall = 0.0676			max =	6		
			Wald chi2(22) =	328.53		
corr(u_i, X) = 0 (assumed)			Prob > chi2 =	0.0000		
			(Std. Err. adjusted for 4574 clusters in patient_id)			
		Robust				
encounter_cc	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
diabetes	1.769222	0.3029229	5.84	0	1.175504	2.36294
age	0.0058583	0.0055131	1.06	0.288	-0.0049471	0.0166637
male	-0.8730805	0.1390204	-6.28	0	-1.145555	-0.6006055
hypertension	0.9878792	0.1369033	7.22	0	0.7195537	1.256205
hyperlipidem	0.3125787	0.1201334	2.6	0.009	0.0771217	0.5480358
ihd	1.270014	0.2350626	5.4	0	0.8092998	1.730728
cerebrovascu	0.8214129	0.5254952	1.56	0.118	-0.2085387	1.851364
bodyweight	0.0035487	0.0027673	1.28	0.2	-0.0018752	0.0089726
ldl_value	-0.1313221	0.065227	-2.01	0.044	-0.2591647	-0.0034795
hdl_value	-0.3449649	0.2015868	-1.71	0.087	-0.7400677	0.0501379
sbp	-0.0010657	0.0052729	-0.2	0.84	-0.0114004	0.009269
dbp	-0.0031535	0.0081897	-0.39	0.7	-0.0192049	0.012898
yr10	0.4485827	0.1509399	2.97	0.003	0.1527459	0.7444195
yr11	-0.2230066	0.1565799	-1.42	0.154	-0.5298975	0.0838843
yr12	0.3145434	0.1443027	2.18	0.029	0.0317153	0.5973714
yr13	0.2712873	0.1449779	1.87	0.061	-0.0128641	0.5554387
yr14	0.0721919	0.1506371	0.48	0.632	-0.2230514	0.3674352
diabetes10	-0.4879445	0.3279805	-1.49	0.137	-1.130774	0.1548855
diabetes11	-0.2022106	0.3874736	-0.52	0.602	-0.9616448	0.5572237
diabetes12	-0.5227756	0.3620912	-1.44	0.149	-1.232461	0.1869102
diabetes13	-0.9504391	0.3512653	-2.71	0.007	-1.638906	-0.2619716
diabetes14	-0.8157181	0.3523214	-2.32	0.021	-1.506255	-0.1251808
_cons	6.41719	0.7430325	8.64	0	4.960873	7.873507

Drug Models for those with diabetes

Drug Model #1 – Diabetic Population

Table 37: Odds of insulin usage for those with diabetes, all covariates included (Drug Model #1)

Insulin						
Logistic regression			Number of obs	=	1545	
			Wald chi2(20)	=	187.6	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-605.89576	Pseudo R2	=	0.1713	
		Robust				
insulin	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.9770607	0.0078961	-2.87	0.004	0.9617066	0.9926599
male	0.8222715	0.1341971	-1.2	0.231	0.5971682	1.132228
hba1c_value	1.793882	0.1453416	7.21	0	1.530485	2.102611
fbs_value	1.006346	0.0415898	0.15	0.878	0.9280458	1.091253
lipid_count	1.017948	0.0096114	1.88	0.06	0.9992835	1.036962
tc_value	1.039037	0.2237816	0.18	0.859	0.6812466	1.584739
hypertension	0.640778	0.1020822	-2.79	0.005	0.4689245	0.8756132
hyperlipidemia	1.054207	0.1846444	0.3	0.763	0.74789	1.485983
ihd	1.577589	0.280007	2.57	0.01	1.114073	2.233953
cerebrovascular_disease	0.6519236	0.3457735	-0.81	0.42	0.2305304	1.843594
bodyweight	1.003752	0.0032322	1.16	0.245	0.9974372	1.010107
ldl_value	0.5940118	0.1374564	-2.25	0.024	0.3774192	0.9349021
hdl_value	1.673543	0.5194053	1.66	0.097	0.9108683	3.074808
sbp	1.020769	0.0081634	2.57	0.01	1.004893	1.036895
dbp	0.9498107	0.0119596	-4.09	0	0.9266573	0.9735428
yr10	0.9192578	0.2487475	-0.31	0.756	0.5408858	1.562317
yr11	0.8081641	0.2305336	-0.75	0.455	0.4620503	1.413546
yr12	0.7969823	0.1981379	-0.91	0.361	0.4895887	1.297376
yr13	0.6919112	0.1687748	-1.51	0.131	0.4289637	1.116041
yr14	0.7016818	0.1688496	-1.47	0.141	0.4378354	1.124526
_cons	0.0376642	0.0476507	-2.59	0.01	0.0031552	0.4495978

Drug Model #2 – Diabetic Population

Table 38: Odds of metformin usage for those with diabetes, all covariates included (Drug Model # 2)

Metformin						
Logistic regression			Number of obs	=	1545	
			Wald chi2(20)	=	140.57	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-977.9473	Pseudo R2	=	0.0856	
		Robust				
metformin	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.9971084	0.005571	-0.52	0.604	0.986249	1.008087
male	1.015181	0.1227346	0.12	0.901	0.8010023	1.286628
hba1c_value	1.583318	0.0978994	7.43	0	1.40261	1.787308
fbs_value	0.9553601	0.0296193	-1.47	0.141	0.899036	1.015213
lipid_count	0.9867196	0.0076252	-1.73	0.084	0.9718872	1.001778
tc_value	1.473297	0.2599122	2.2	0.028	1.042618	2.081878
hypertension	1.114823	0.1282854	0.94	0.345	0.889726	1.39687
hyperlipidemia	0.8782178	0.1120121	-1.02	0.309	0.6839681	1.127635
ihd	0.9327589	0.1340043	-0.48	0.628	0.703853	1.236109
cerebrovascular_disease	1.321621	0.484945	0.76	0.447	0.6438342	2.712939
bodyweight	1.001878	0.0025986	0.72	0.469	0.9967978	1.006984
ldl_value	0.5568096	0.1103127	-2.96	0.003	0.3776334	0.8209999
hdl_value	0.471902	0.1063894	-3.33	0.001	0.3033541	0.7340973
sbp	0.9853427	0.0057378	-2.54	0.011	0.9741608	0.996653
dbp	1.024944	0.0093167	2.71	0.007	1.006846	1.043368
yr10	1.121721	0.214599	0.6	0.548	0.770974	1.632038
yr11	1.091556	0.2282237	0.42	0.675	0.7245625	1.644433
yr12	0.8276863	0.151595	-1.03	0.302	0.5780479	1.185135
yr13	0.675215	0.1232713	-2.15	0.031	0.4721082	0.9657008
yr14	0.4967415	0.0896429	-3.88	0	0.3487555	0.7075217
_cons	0.1158694	0.1071496	-2.33	0.02	0.0189158	0.7097625

Drug Model #3 – Diabetic Population

Table 39: Odds of sulfonylurea usage for those with diabetes, all covariates included (Drug Model # 3)

Sulfonylurea						
Logistic regression			Number of obs	=	1545	
			Wald chi2(20)	=	135.95	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-748.06467	Pseudo R2	=	0.0883	
		Robust				
sulfonylurea	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	1.019736	0.0068198	2.92	0.003	1.006457	1.033191
male	1.136516	0.1727324	0.84	0.4	0.8437359	1.530893
hba1c_value	1.63816	0.1067106	7.58	0	1.441812	1.861247
fbs_value	0.936912	0.032635	-1.87	0.061	0.8750831	1.003109
lipid_count	0.9881413	0.0093893	-1.26	0.209	0.9699089	1.006716
tc_value	1.460744	0.2665111	2.08	0.038	1.021582	2.088694
hypertension	1.075832	0.1444968	0.54	0.586	0.8268335	1.399815
hyperlipidemia	1.075538	0.168302	0.47	0.642	0.7914586	1.461582
ihd	0.9212002	0.1557612	-0.49	0.627	0.6613457	1.283156
cerebrovascular_disease	1.002393	0.383709	0.01	0.995	0.4733736	2.122619
bodyweight	0.9960076	0.003306	-1.21	0.228	0.9895489	1.002508
ldl_value	0.4717763	0.0982711	-3.61	0	0.3136395	0.7096456
hdl_value	0.4296675	0.1230651	-2.95	0.003	0.2450935	0.7532396
sbp	0.9951167	0.0065217	-0.75	0.455	0.9824161	1.007981
dbp	1.004457	0.0109062	0.41	0.682	0.9833067	1.026062
yr10	1.056751	0.2330839	0.25	0.802	0.6858452	1.628243
yr11	0.9363473	0.2252445	-0.27	0.785	0.5843525	1.500372
yr12	0.8559777	0.1846675	-0.72	0.471	0.5608224	1.30647
yr13	0.6425335	0.1434472	-1.98	0.048	0.4148231	0.9952418
yr14	0.6316759	0.1379881	-2.1	0.035	0.4116721	0.9692531
_cons	0.0234696	0.0265519	-3.32	0.001	0.0025557	0.2155248

Drug Model #4 – Diabetic Population

Table 40: Odds of other oral hypoglycemic usage for those with diabetes, all covariates included (Drug Model # 4)

Other Oral Hypoglycemic						
Logistic regression			Number of obs	=	1545	
			Wald chi2(20)	=	83.09	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-322.12734	Pseudo R2	=	0.0976	
		Robust				
other_oral_hypoglycemic	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	1.01757	0.0101655	1.74	0.081	0.9978396	1.03769
male	1.787216	0.4537857	2.29	0.022	1.086555	2.939698
hba1c_value	1.404167	0.1263388	3.77	0	1.177152	1.674962
fbs_value	0.971534	0.0542752	-0.52	0.605	0.8707735	1.083954
lipid_count	0.9841517	0.0180102	-0.87	0.383	0.9494779	1.020092
tc_value	1.209167	0.3012859	0.76	0.446	0.7419831	1.97051
hypertension	1.56953	0.386206	1.83	0.067	0.9689894	2.542262
hyperlipidemia	0.8666544	0.2094959	-0.59	0.554	0.5396168	1.391895
ihd	0.3889033	0.1223253	-3	0.003	0.2099449	0.7204069
cerebrovascular_disease	0.9979353	0.6769718	0	0.998	0.2640406	3.771673
bodyweight	1.015578	0.0038398	4.09	0	1.00808	1.023132
ldl_value	0.6860063	0.1893097	-1.37	0.172	0.3994213	1.178216
hdl_value	0.8695617	0.3610342	-0.34	0.736	0.38538	1.962057
sbp	0.9686334	0.0113592	-2.72	0.007	0.9466237	0.9911548
dbp	0.9874897	0.0178675	-0.7	0.487	0.9530837	1.023138
yr10	1.304793	0.4376597	0.79	0.428	0.6761263	2.517999
yr11	0.8620807	0.3220885	-0.4	0.691	0.4144996	1.792965
yr12	0.540437	0.2062386	-1.61	0.107	0.2558081	1.141763
yr13	0.379906	0.15315	-2.4	0.016	0.172399	0.8371776
yr14	0.5067501	0.1893331	-1.82	0.069	0.2436498	1.053954
_cons	0.1030419	0.2118303	-1.11	0.269	0.0018329	5.792789

Drug Model #5 - Diabetic Population

Table 41: Odds of insulin usage for those with diabetes, excluding covariates (Drug Model # 5)

Logistic regression			Number of obs	=	16960	
			Wald chi2(12)	=	220.67	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-6836.7193	Pseudo R2	=	0.0176	
		Robust				
insulin	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.9827742	0.0015615	-10.94	0	0.9797185	0.9858394
male	0.7953981	0.0357476	-5.09	0	0.7283312	0.8686406
lipid_count	1.024484	0.0036896	6.72	0	1.017278	1.031741
hypertension	0.9871008	0.0458717	-0.28	0.78	0.9011669	1.081229
hyperlipidemia	0.9958996	0.047147	-0.09	0.931	0.9076505	1.092729
ihd	1.533914	0.0871539	7.53	0	1.372263	1.714607
cerebrovascular_disease	1.392822	0.1928754	2.39	0.017	1.061751	1.827125
yr10	1.063662	0.0984385	0.67	0.505	0.8872126	1.275204
yr11	1.131489	0.1015371	1.38	0.169	0.948999	1.349072
yr12	1.063938	0.0924824	0.71	0.476	0.8972755	1.261556
yr13	0.957003	0.0823225	-0.51	0.609	0.8085222	1.132751
yr14	0.9321148	0.0791368	-0.83	0.408	0.7892274	1.100872
_cons	0.4189164	0.0484536	-7.52	0	0.3339442	0.5255099

Drug Model # 6 – Diabetic Population

Table 42: Odds of metformin usage for those with diabetes, excluding covariates (Drug Model # 6)

Logistic regression			Number of obs	=	16960	
			Wald chi2(12)	=	445.1	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-11271.188	Pseudo R2	=	0.0211	
		Robust				
metformin	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.9921953	0.0010778	-7.21	0	0.9900851	0.99431
male	1.019982	0.0325324	0.62	0.535	0.9581718	1.08578
lipid_count	1.022434	0.0034235	6.63	0	1.015746	1.029166
hypertension	1.055956	0.0350562	1.64	0.101	0.989435	1.12695
hyperlipidemia	1.605581	0.0544184	13.97	0	1.502388	1.715861
ihd	0.9265745	0.039491	-1.79	0.074	0.8523182	1.0073
cerebrovascular_disease	0.6546094	0.0726129	-3.82	0	0.5266987	0.8135838
yr10	0.8982368	0.0591504	-1.63	0.103	0.7894739	1.021983
yr11	0.9249987	0.0590562	-1.22	0.222	0.8161998	1.048301
yr12	0.790361	0.0488964	-3.8	0	0.7001082	0.8922485
yr13	0.6698889	0.040773	-6.58	0	0.5945578	0.7547645
yr14	0.5965319	0.0360471	-8.55	0	0.5299044	0.6715368
_cons	1.006086	0.0836054	0.07	0.942	0.8548705	1.184049

Drug Model # 7 – Diabetic Population

Table 43: Odds of sulfonylurea usage for those with diabetes, excluding covariates (Drug Model # 7)

Logistic regression			Number of obs	=	7616	
			Wald chi2(13)	=	151.58	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-3895.2537	Pseudo R2	=	0.0211	
		Robust				
sulfonylurea	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	1.007313	0.0024014	3.06	0.002	1.002618	1.012031
male	1.069549	0.0615342	1.17	0.243	0.9554951	1.197216
lipid_count	0.9965371	0.0038298	-0.9	0.367	0.9890591	1.004072
tc_value	0.7475653	0.0245479	-8.86	0	0.700968	0.7972603
hypertension	1.045558	0.0613307	0.76	0.448	0.9320047	1.172947
hyperlipidemia	1.164654	0.0724301	2.45	0.014	1.031004	1.315628
ihd	1.09374	0.077037	1.27	0.203	0.9527089	1.255649
cerebrovascular_disease	0.9795286	0.1903615	-0.11	0.915	0.6692597	1.433638
yr10	0.8359696	0.0867335	-1.73	0.084	0.6821449	1.024482
yr11	0.8549683	0.0922723	-1.45	0.147	0.6919651	1.056369
yr12	0.8224131	0.0806369	-1.99	0.046	0.6786259	0.9966658
yr13	0.7474528	0.0720801	-3.02	0.003	0.6187265	0.9029606
yr14	0.682234	0.0667219	-3.91	0	0.5632311	0.8263806
_cons	0.6501868	0.1513036	-1.85	0.064	0.4120565	1.025934

Drug Model # 8 – Diabetic Population

Table 44: Odds of other oral hypoglycemic usage for those with diabetes, excluding covariates (Drug Model # 8)

Logistic regression			Number of obs	=	16960	
			Wald chi2(12)	=	121.77	
			Prob > chi2	=	0	
Log pseudolikelihood	=	-3783.9095	Pseudo R2	=	0.0159	
		Robust				
other_oral_hypoglycemic	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.9933426	0.0020088	-3.3	0.001	0.9894133	0.9972875
male	1.465039	0.0974811	5.74	0	1.285914	1.669117
lipid_count	0.9931763	0.0051966	-1.31	0.191	0.9830432	1.003414
hypertension	1.081464	0.0759126	1.12	0.265	0.9424595	1.240971
hyperlipidemia	1.612005	0.1206892	6.38	0	1.391996	1.866788
ihd	0.809639	0.0741085	-2.31	0.021	0.6766726	0.9687334
cerebrovascular_disease	0.5354717	0.1520586	-2.2	0.028	0.3069161	0.9342289
yr10	0.9069782	0.1123165	-0.79	0.43	0.7115207	1.156129
yr11	0.7662188	0.0933234	-2.19	0.029	0.603502	0.9728074
yr12	0.6419747	0.0783072	-3.63	0	0.5054631	0.8153543
yr13	0.6621141	0.0781553	-3.49	0	0.5253611	0.8344643
yr14	0.6333848	0.0737037	-3.92	0	0.5042172	0.7956418
_cons	0.080985	0.0123797	-16.44	0	0.0600186	0.1092756