Evidence-to-recommendation table

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds(1). Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Diabetes mellitus is a chronic condition that occurs in approximately 8.5% of the adult population and its prevalence increases with age. The presence of late-life diabetes has been found to be linked to an increased risk of dementia(2)	Diabetes is a well established risk factor for cognitive decline and dementia
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** *Desirable effects* No data was available for MCI. For cognitive function the volume of evidence is low (2 RCTs) and the quality of evidence is moderate. For incident dementia the volume of evidence is low (1 RCT) and the quality of evidence is very low. No meta-analyses were conducted. For cognitive function, the review states “little to no difference between intensive and standard treatment regimens on the MMSE” but no numerical data is provided. For incident dementia, the review reports a non-significant effect of intense glycaemic control (RR = 1.27, 95% CI .087 to 1.85). An average of 500 patients would have to receive intensive glycaemic control for treatment of diabetes instead of standard care for one additional patient to develop dementia. Number to harm (NNH) = 500	Tuligenga(3) conducted a meta-analysis of RCTs comparing intensive versus standard glycaemic control and reported that there was no statistically significant difference in cognitive decline between the intensive glycaemic control group and the standard glycaemic control group (SDM = 0.02; 95% CI -0.03 to 0.08). They also noted that there was significant heterogeneity across individual studies (I2 = 68%). Aresoa et al. (4)narratively reported there was no good evidence that the intensity of glycaemic control or differences in pharmacological treatments for diabetes had any effect on preventing or delaying cognitive impairment.

	Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention *Desirable effects* No data for MCI, incident dementia. For cognitive function, volume of evidence is low, quality of evidence is very low and the findings were mixed. No meta-analysis was conducted, and there was no robust data on clinical significance.	With regards to lifestyle interventions, one review (5) found mixed results regarding the impact of physical activity on cognitive functioning in adults with diabetes. The AHRQ report (6) concluded that overall, there was a lack of evidence showing that treatments for diabetes had an impact on the incidence of MCI or dementia. A review of cross-sectional and longitudinal studies (5) found that physical training may help improve the cognitive outcomes of individuals with type 2 diabetes.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** *Undesirable effects:* No evidence on quality of life, functional level or drop outs. For adverse events the volume of evidence is low with two RCTs reporting hypoglycaemia. Quality of evidence is very low. There were more hypoglycaemic episodes in the intensively treated group RR = 2.18 (1.52 to 3.14). On average 55.6 patients would have to receive intensive glycaemic control for treatment of diabetes instead of standard care for one additional patient to have a hypoglycaemic episode. NNH = 55.6. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** *Undesirable effects:* No data adverse events, functional levels, or dropouts.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** **Findings:** Certainty of the evidence is moderate for cognitive function and very low for incident dementia, which showed intensive as opposed to standard glycaemic control has an unclear effect on cognitive function and no effect on dementia. The certainty of evidence for adverse events is very low, showing intensive glycaemic control Increases risk of hypoglycaemic events. No evidence for MCI was available. No evidence on quality of life or functional outcomes or drop-out rates. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** **Findings:** Certainty of evidence is very low. The effect of physical activity on cognitive function is unclear: No evidence for MCI or dementia. No adverse events for diet and lifestyle.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009(7) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(8)and the United Kingdom(9)(UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, of view cognitive decline favourably.	Additional sources like the Saga Survey(10) and Alzheimer's Research UK(11) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)

	Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention:** May favour standard glycaemic control because intense glycaemic control has no effect on cognitive function but may result in increased episodes of hypoglycaemia. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** Unable to make conclusive comment due to mixed findings and very low quality evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	For the treatment of diabetes in the form of medications for glycaemic, no additional resources are needed because the evidence favours standard care over intensive glycaemic control. However, see additional considerations for a list of medications can be used to treat diabetes. The costs are dependent the drug used. For the treatment of diabetes in the form of diet and lifestyle interventions, only one review was included and it examined the effects of regular physical activity on the cognitive performance of patients with type II diabetes. No data on resources required were reported.	The WHO(12)recommendations for antidiabetic medicines are listed below. The prices are taken from the International Drug Price Indicator Guide (http://mshpriceguide.org/en/home/) and are listed as price per unit. · Gliclazide (glibenclamide not suitable above 60 years) è Solid oral dosage form: (controlled-release tablets) 30 mg; Median Price US$ (Supplier/Buyer) = not listed/0.0350; 60 mg (price not listed);80 mg; Median Price US$ (Supplier/Buyer) = 0.0591/0.0455. · Glucagon è Injection: 1 mg/ mL.; Median Price US$ (Supplier/Buyer) = not listed/25.7458 · Insulin injection (soluble) è Injection: 40 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = not listed/0.2600; 100 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = 0.8834/0.4919 · Intermediate-acting insulin è Injection: 40 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = not listed/0.2600; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension or isophane insulin); Median Price US$ (Supplier/Buyer) = 0.8834/0.3603 · Metformin è Tablet: 500 mg (hydrochloride); Median Price US$ (Supplier/Buyer) = 0.0169/0.0262 *Complementary List* · Metformin Tablet: 500 mg (hydrochloride)
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Antidiabetic medication and physical activity are already being recommended as treatment option for patients with diabetes. Antidiabetic medications are included in the WHO model list of essential medicines(12) and their costs are listed in the International Drug Price Indicator Guide(13). Physical activity interventions are not well defined and their costs can vary depending on a range of factors (e.g. equipment needed, length of intervention, guided vs unguided etc).	The WHO factsheet on diabetes (http://www.who.int/en/news-room/fact-sheets/detail/diabetes) states that: "Treatment of diabetes involves diet and physical activity along with lowering blood glucose and the levels of other known risk factors that damage blood vessels. Tobacco use cessation is also important to avoid complications. Interventions that are both cost-saving and feasible in developing countries include: · blood glucose control, particularly in type 1 diabetes. People with type 1 diabetes require insulin, people with type 2 diabetes can be treated with oral medication, but may also require insulin; · blood pressure control; and foot care. Other cost saving interventions include: · screening and treatment for retinopathy (which causes blindness) · blood lipid control (to regulate cholesterol levels) · screening for early signs of diabetes-related kidney disease and treatment."
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Various medicinal and diet/lifestyle interventions can be used to treat diabetes and costs are dependent the intervention administered. However there is evidence to show that antidiabetic interventions can be cost-effective in the treatment of diabetes6 (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.	The cost effectiveness of antidiabetic interventions in adults (retrieved from the WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010)(14) p.64): · Intervention = Life style intervention for type 2 diabetes Cost Effectiveness = 60 US$/QALY · Intervention = Optimal Glycemic control in clinic Cost Effectiveness = 1810 US$/QALY (SSA) · Intervention = ACE inhibitor for blood pressure control Cost Effectiveness = 620 US$/QALY (EAP) For more information: 'Best buys' and other recommended interventions to address noncommunicable diseases (NCDs) http://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17.9-eng.pdf?sequence=1
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons(15)studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	Depends on access to treatment especially in low- and middle-income countries

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both antidiabetic medication and physical activity are already being used as treatment options for patients with diabetes. The evidence reviewed here shows that treatment for diabetes in the form of medications for glycaemic control has an unclear effect on cognitive function, no effect on dementia and increases risk of hypoglycaemic events. As such, the acceptability of antidiabetic medication interventions for reducing the risk of and cognitive decline and/or dementia may vary across stakeholders.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, both standard care and intensive glycaemic control are already being used in diabetic populations currently. Physical activity is also already being recommended as a treatment option for diabetes.	

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