Title: Long-Term Health and Economic Impact of a Low-Intensity Lifestyle Program to Prevent Type 2 Diabetes Mellitus in Germany: A Simulation Study.

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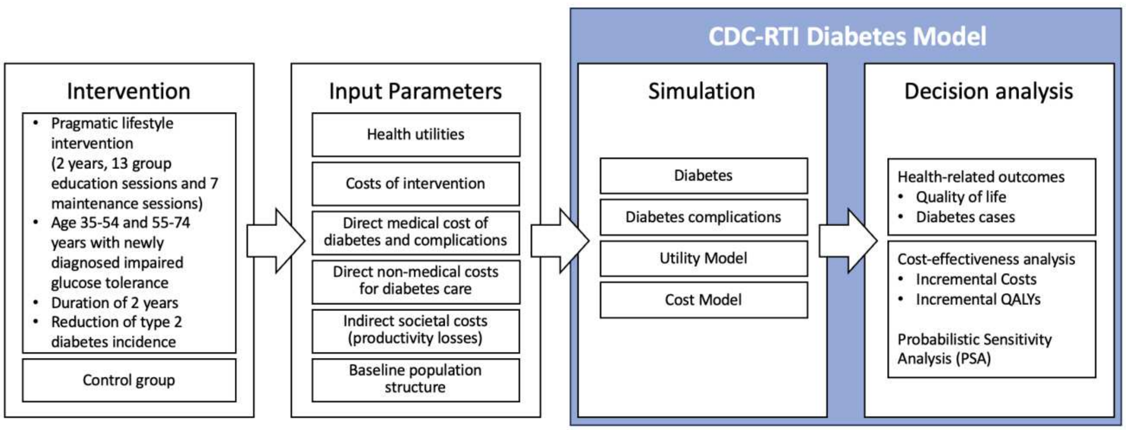
Supplementary Materials



Supplementary Figure 1 The workflow of the analysis.

Supplementary Table 1 Key model parameter values used for simulating the long-term health and economic impacts of a lifestyle intervention for preventing type 2 diabetes in Germany

Description	Value	Source	Comments
Age- and sex-adjusted cost ratio of "intermediate hyperglycaemia" vs "no diabetes" in Germany	1.09	(1)	
Annual cost of health care for a person without type 2 diabetes, in € (2015)	2196.00 [Gamma distribution, SE: 555.93]	(2)	Costs of health care for a person with HbA1c are calculated with the use of the cost ratio.
Annual cost of health care for a person with HbA1c in the at-risk range with no treatment, in € (2015)	2393.64 [Gamma distribution, SE: 597.05]		
Annual cost of health care for a person with type 2 diabetes, in € (2015)	4727.00 [Gamma distribution, SE: 547.75]		
Annual patient time costs for a person with type 2 diabetes attributable to self-management, in € (2014)	2122.00	(3)	
Annual indirect societal costs caused by productivity losses per a person with type 2 diabetes, in € (2011)	4103.00	(4)	The costs were assigned to all individuals younger than 65 years old, the mean age of retirement in Germany in 2020 (5)
Cost of pragmatic lifestyle intervention Year 1, in €	228.39 [Uniform distribution, min: 114.20, max: 342.59]	(6)	The Personal Social Services Research Unit costs applied to activities outlined as part of a recommended lifestyle program in NICE guidance. The costs in Pound Sterling were converted to € by applying purchasing power parities conversion in 2015. Reference year: 2015
Cost of pragmatic lifestyle interventions Year 2, in €	89.83 [Uniform distribution, min: 44.92, max: 134.75]		
Utility decrement for onset of type 2 diabetes	-0.035	(7)	The health-related quality of life was assessed by using the EuroQol five-dimensional five-level questionnaire (EQ-5D-5L).
Utility decrements for complications: Chronic heart failure	-0.080		
Utility decrements for complications: Stroke	-0.069		
Utility decrements for complications: Myocardial Infarction	-0.014		
Utility decrements for complications: Neuropathy	-0.093		
Utility decrements for complications: Blindness	-0.101		

Utility decrements for complications: Nephropathy	-0.062		
Utility decrements for complications: Diabetic foot	-0.037		
Annual discount rate for costs	0.035	(8,9)	
Discount rate for effectiveness	0.035		
The relative risk of death with type 2 diabetes, male	2.3	(10)	The age- and sex-specific relative risks are representative of the general population age 65-90 years in Germany. We assume that the same relative risks are valid in age groups 35-54 and 55-74.
The relative risk of death with type 2 diabetes, female	3		
Incidence rate of type 2 diabetes among 35-54 years old with HbA1c in at-risk range, per 1000 person-year	7.05		The risk was obtained using the incidence rate ratio of diabetes in different age groups (11) and the estimated probability of type 2 diabetes in 55-74 age group from KORA S4-F4 follow-ups (12)
Incidence rate of type 2 diabetes among 55-74 years old with HbA1c in at-risk range, per 1000 person-year	10.5		Estimated from KORA S4-F4 follow-ups (12) by assessing the new cases of type 2 diabetes and life years under the risk in the follow-up waves S4 and F4 for persons 55-74 years old at the baseline
The relative risk of type 2 diabetes in participant undertaking pragmatic lifestyle program in years 1 and 2	0.74 [Log-normal distribution, median: 0.735]	(13)	The value was taken from the meta-analysis of randomized clinical trials. We assumed relative risk reduction equal for IFG, IGT and HbA1c as insufficient primary studies to analyze differences.
Total number of individuals in the age group 35-54 in Germany	22,181,829	(14)	The general population in the reference year 2020
Total number of individuals in the age group 55-74 in Germany	20,918,203		
Prevalence of high-risk individuals defined by HbA1c at range 6.0-6.4 %, 35-54 years old, Germany	10.4%	(15)	
Prevalence of high-risk individuals defined by HbA1c at range 6.0-6.4 %, 55-74 years old, Germany	29.5%		Estimated from KORA S4 follow-up (12)
Yearly expenditure on diabetes in Germany, in 2021, €	4,6251.3 Million	(16)	The total diabetes-related expenditures in 2021

Notes: IFG - impaired fasting glycaemia; IGT - impaired glucose tolerance; KORA - Cooperative Research in the Region of Augsburg; SE – standard deviation.

Supplementary Table 2: Health utility decrement associated with diabetes and diabetes complications

Factors	**Coefficients**
Diabetes Intercept: onset to diagnosis	0.700
Diabetes Intercept: early diagnosis to clinical diagnosis	0.700
Diabetes Intercept: after clinical diagnosis	0.700
Intermediate hyperglycaemia Intercept	0.717
No diabetes Intercept	0.722
Female	-0.027
Hypertension	-0.001
Blind	-0.100
Nephropathy	-0.064
End Stage Renal Disease (ESRD)	-0.064[*]
Peripheral Neuropathy	-0.092
Foot Ulcer	-0.037
Lower Extremity Amputation	-0.037
History of CA/MI	-0.014
Congestive heart failure	-0.080
Stroke	-0.069
BMI >= 30.0	-0.040

* - assumed equal to nephropathy; no data in the original study

Supplementary Table 3: Cumulative type 2 diabetes incidence and diabetes risk reduction for individual participation in 10 years and at the end of the simulation

	No intervention		Pragmatic lifestyle intervention			
	Cumulative incidence type 2 diabetes, %		Cumulative incidence type 2 diabetes, %		Relative risk reduction, %	
	After 10 years	At the end of the simulation	After 10 years	At the end of the simulation	After 10 years	At the end of the simulation
Cohort 35-54 years old	6.68	21.05	6.16	20.61	7.78	2.09
Cohort 55-74 years old	9.00	16.77	8.27	16.10	8.11	4.00

Supplementary Table 4 The distribution parameters of incremental cost, effects and cost-effectiveness ratios relative to no intervention for individual participants in a prevention program over a lifetime perspective from probabilistic sensitivity analysis (health care system perspective)

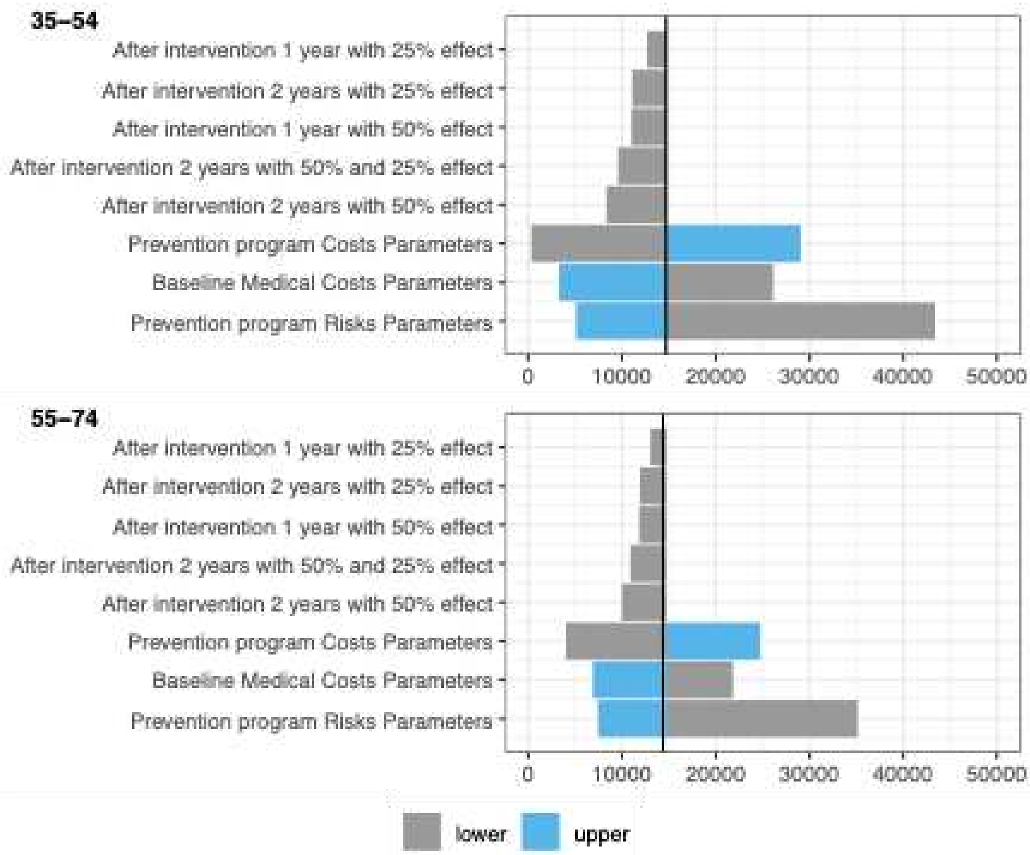
	Mean	**Median**	**Standard deviation**	**2.5% quantile**	**97.5% quantile**
Cohort 35-54 years old					
Effect vs no intervention (QALYs), incremental	0.01	0.01	0.003	0.01	0.02
Costs vs no intervention (€, 2020), incremental	165.39	172.02	98.83	-42.27	349.72
ICER (€/QALY)	18,071.33	15,602.56	27,896.28	-2,904.53	46,668.14
Cohort 55-74 years old					
Effect vs no intervention (QALYs), incremental	0.02	0.02	0.004	0.01	0.02
Costs vs no intervention (€, 2020), incremental	223.17	224.72	90.05	44.59	402.92
ICER (€/QALY)	15,999.64	14,729.45	9,963.87	2,543.01	36,954.60

Supplementary Table 5: Incremental cost-effectiveness ratios and cost-effectiveness relative to no intervention for individual participants in a prevention program over a lifetime perspective (health care system perspective)

Length of intervention			Incremental cost-effectiveness ratios (ICER) (relative to no intervention)					WPT needed to achieve a probability of cost-effectiveness		
	Costs vs no intervention (€, 2020), incremental	Effect vs no intervention (QALYs), incremental	ICER (€/QALY)	Probability ICER < 20,000 €/QALY, %	Probability ICER < 50,000 €/QALY, %	Probability ICER < 100,000 €/QALY, %	Probability ICER < 0 €/QALY, %	>= 50%	>= 75%	>= 95%
Cohort 35-54 years old										
Health care system perspective	165.24	0.011	14,689.76	65.4	98.0	99.8	5.1	15,602.5	23,849.7	40,390.2
Societal perspective	-42.80	0.011	-3,804.53							
Cohort 55-74 years old										
Health care system perspective	220.88	0.015	14,372.40	74.0	99.2	99.9	0.4	14,729.5	20,235.4	31,745.4
Societal perspective	70.36	0.015	4,578.17							

Supplementary Table 6: Incremental cost-effectiveness ratios and cost-effectiveness relative to no intervention for individual participants in a prevention program over a lifetime perspective with alternative assumptions on epidemiological and economic parameters (health care system perspective)

Scenario	Cohort 35-54 years old			Cohort 55-74 years old		
	Life-time incremental costs from a health care system perspective (€, 2020)	Lifetime incremental QALYs	ICER (€/QALY) from a health care system perspective	Costs vs no intervention (€, 2020), incremental	Lifetime incremental QALYs	ICER (€/QALY) from a health care system perspective
Base case	96.08	0.02	14,689.76	220.88	0.02	14,372.40
Low Prevention program Costs Parameters	3.76	0.01	333.99	61.45	0.02	3,998.28
High Baseline Medical Costs Parameters	36.56	0.01	3,250.32	106.00	0.02	6,897.27
High Prevention program Risks Parameters	86.42	0.02	5,117.34	172.06	0.02	7,454.20
After intervention 2 years with 50% effect	121.57	0.01	8,302.85	197.62	0.02	10,011.61
After intervention 2 years with 50% and 25% effect	132.06	0.01	9,562.64	202.99	0.02	10,866.54
After intervention 1 year with 50% effect	142.56	0.01	10,983.86	208.35	0.02	11,824.25
After intervention 2 years with 25% effect	143.41	0.01	11,078.48	209.25	0.02	11,921.24
After intervention 1 year with 25% effect	153.90	0.01	12,704.49	214.62	0.02	13,011.33
Low Baseline Medical Costs Parameters	293.92	0.01	**26,129.20**	335.76	0.02	**21,847.50**
High Prevention program Costs Parameters	326.72	0.01	**29,045.50**	380.31	0.02	**24,746.50**
Low Prevention program Risks Parameters	243.92	0.01	**43,407.50**	269.57	0.01	**35,127.70**



Supplementary Figure 2 Tornado diagram of Incremental cost-effectiveness ratios relative to no intervention for individual participants in a prevention program over a lifetime perspective with alternative assumptions on epidemiological and economic parameters (health care system perspective).

Supplementary Table 7: Incremental cost-effectiveness ratios relative to no intervention with different cost structures at the end of the simulation (lifetime perspective)

Cost perspective	**35-54 years**	**55-74 years**
Only direct medical costs (€, 2020)	14,689.76	14,372.40
Direct medical + Indirect societal costs (€, 2020)	11,128.60	23,105.36
Direct medical + Non-medical (patient time) costs (€, 2020)	-243.36	14,368.62
Direct medical + Non-medical (patient time) + Indirect societal costs (€, 2020)	-3,804.53	4,578.71

Supplementary Table 8 Estimated cumulative incidence of type 2 diabetes for control and intervention groups by implementing a nation-wide diabetes prevention program In Germany

Population at high risk of developing type 2 diabetes		Cumulative incidence of type 2 diabetes in control group, lifetime	Cumulative incidence of type 2 diabetes in intervention group, lifetime	Lifetime reduction in incident cases of type 2 diabetes, cases
Total N	Mean % of participating			
Cohort 35-54 years				
2,308,625	100%	1,298,752	1,271,964	26,788
1,154,312	50%	649,376	635,982	13,394
577,156	25%	324,688	317,991	6,697
230,862	10%	129,875	127,196	2,679
115,431	5%	64,937	63,598	1,339
Cohort 55-74 years				
6,170,870	100%	387,101	371,781	15,319
3,085,435	50%	193,550	185,891	7,660
1,542,718	25%	96,775	92,945	3,830
617,087	10%	38,710	37,178	1,532
30,854	5%	19,355	18,589	766

Assumptions

Conducting this study, we made some important assumptions, which were mostly conservative. First, we assumed that the effect of the lifestyle intervention taken from a systematic review (13) was similar in all subgroups. In the original review, progression to type 2 diabetes appeared to be independent of age and ethnicity but increased with a higher percentage of male participants. At the same time, participants with overweight saw bigger gains in terms of the reduction of type 2 diabetes. In our analysis, all participants were assumed to be “White” and not obese (BMI < 30 kg/m2) which reflects the German population, according to population-based studies (12). The percentage of males reflected the German population as well. We did not expect significant variations of the intervention effect in such a relatively homogeneous population. However, further research of how the intervention outcomes is modified depending on participant characteristics may increase the efficacy of tailored advice, for example by focusing on specific sub-groups with a higher risk of a particular complications, thereby improving cost-effectiveness (17,18).

There is a lack of evidence on the incidence of type 2 diabetes in the population aged 35-54 with intermediate hyperglycaemia in Germany. To derive the incidence of diabetes in this cohort, we used incidence rate ratios from a study of the rate of progression to diabetes (11). We must be aware that this combined estimate might not accurately reflect reality. Further research on diabetes incidence in Germany is needed with the focus on younger cohorts of people with intermediate hyperglycaemia.

We also assumed equal risks of diabetes-related death in all subgroups. While there is no difference in diabetes-related mortality rate ratios between men and women in Germany (19), the age-specific mortality rate ratios are reported higher for younger participants in German studies (20,21), which may lead to lower ICER in the economic evaluation and result in higher probability of cost-effectiveness.

We did not implement in the model direct effects of the intervention on mortality or incidence of diabetes complications, either, because we are not aware of any evidence that the pragmatic lifestyle intervention directly affects all-cause mortality or incidence of late state complications.

Regarding the equal mortality risks in persons with normoglycemia and with intermediate hyperglycaemia supposed in our simulation, there is some contradictory evidence. People with intermediate hyperglycaemia have an elevated risk of sudden cardiac death (22). A higher risk of all-cause mortality was detected in both the IFG and IGT based intermediate hyperglycaemia groups but not when intermediate hyperglycaemia was defined with the HbA1c diagnostic criterium (23). In our analysis, the intermediate hyperglycaemia definition was based on HbA1c. Moreover, in the CDC-RTI DM, no diabetes-related complications are assumed for the intermediate hyperglycaemia group and no death from a specific cause, such as a cardiac arrest, is possible.

We did not assume any special screening for intermediate hyperglycaemia but occasional diagnosis under the standard medical care. By varying the participation rate in the public health analysis, that might potentially include the participation in any screening as well, we showed rough scale of expenses and gains.

Adherence of participants to the prevention program was assumed being equivalent to those in real-world setting studies. We may suppose that it might be even lower if implemented in a routine outpatient practice. However, we expect that lower adherence may result in a lower effect of the program; correspondingly, we have shown the consequences of reduced effect in the sensitivity analysis.

Conservatively, we assumed that the effects of the intervention persist only for the intervention period. In general, the assumptions about the effect lasting in modelling studies varied (24), and it was shown that for some interventions, the cost-effectiveness would be 10 times higher (25) if the effectiveness was assumed to be lifelong instead of persisting for one year. Such long-term effects have been demonstrated in the clinical trials (26,27), thus these results are the most conservative.

There is no reversion from intermediate hyperglycaemia to normoglycemia possible in our model due to no solid evidence supporting in pragmatic interventions (28).

Studies have shown that lifestyle intervention participants have higher health utilities than those who do not participate (29). However, we assumed the same utilities in both intervention and routine care scenarios, which renders our estimates even more conservative.

Ogurtsova K, *et al. BMJ Open Diab Res Care* 2024; 12:e004382. doi: 10.1136/bmjdrc-2024-004382

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