Technical Report for The adaptation of the CDC RTI Diabetes model for the Germany settings

Parameter values, assumptions and limitations

Description	Value	Source	Comments
The initial cohort description			
The mean BMI of a cohort: all	27,2	The estimates were derived in the analysis of the baseline KORA S4 (1999-2001)	
The mean BMI of a cohort: NoDM	26,6		
The mean BMI of a cohort: PreDM	27,6		
The mean BMI of a cohort: DM	31,4		
The population structure of newly diagnosed with diabetes	(table can be provided by request)	1. The estimates were derived in the analysis of the baseline KORA S4 (1999-2001) 2. Federal Statistical Office of Germany (Statistisches Bundesamt)	Given by age groups, sex (male/female), cholesterol level (normal/above normal), presence of hypertension (normal/above normal), smoking (yes/no). The distribution was drawn from the marginal distribution by risk factors in the KORA data and the general German population structure.
Percentage of normal level of hypertension in NoDM group	0,56 %	The estimates were derived in the analysis of the baseline KORA S4 (1999-2001)	
Percentage of above normal level of hypertension in NoDM group	2,34 %		
Percentage of normal level of hypertension in PreDM group	28,3 %		
Percentage of above normal level of hypertension in PreDM group	39,8 %		

Diabetes prevalence (%) by age, sex and race	See Table 1	The estimates were derived in the analysis of the baseline KORA S4 (1999-2001)	Diabetes prevalence rates are used to calculate mortality rates for persons without diabetes.
Mean blood pressure (systolic and diastolic) values by age groups in group of normal and above normal hypertension	See Table 2	The estimates were derived in the analysis of the baseline KORA S4 (1999-2001)	
The mortality parameters			
Total mortality rates (per 1 million) by age, sex and race	See Table 3	Human Mortality Database (HMD). Available from: https://www.mortality.org/	Total mortality rates are averaged over years 1999 to 2008 that covering the time period between baseline and the first follow-up wave. All of the raw data used for the HMD for Germany originate from statistical data provided by the Federal Statistical Office in Wiesbaden and the Statistical Offices of the German states.
CVD mortality rates (per 1 million) by age, sex and race	See Table 4	Federal Statistical Office of Germany (Statistisches Bundesamt)	The mortality is standardized to German population 2011. CVD mortality was defined by following ICD10 codes I20-I25 “Ischaemic heart diseases” and I60-I69 “Cerebrovascular diseases”
Diabetic death risk, male	2,3	T. Tönnies, A. Hoyer, and R. Brinks, “Excess mortality for people diagnosed with type 2 diabetes in 2012 – Estimates based on claims data from 70 million Germans,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 28, no. 9, pp. 887–891, Sep. 2018.	The diabetes death risk allows users to set higher mortality rates for persons with diabetes than for persons without diabetes. The age-specific HRs are representative for general population in Germany.
Diabetic death risk, female	3		
Diabetic death risk in DM group	2,6 CI 95% [1,7; 3,8]	Kowall, B., Rathmann, W., Heier, M., Giani, G., Peters, A., Thorand, B., Huth, C., Icks, A., Meisinger, C., “Categories of glucose tolerance and continuous glycemic measures and	
Diabetic death risk in undiagnosed DM group	2,8 CI 95% [1,7;4,4]		

Diabetic death risk in PreDM group	1,1 CI 95% [0,8;1,7]	mortality," *Eur. J. Epidemiol.*, vol. 26, no. 8, pp. 637–645, 2011.	
The disease progression			
Annual DM onset probability, per person-year, in a group of persons with NoDM	0,00267 CI 95% [0,002013; 0,003477]	The estimates were derived in the analysis of the KORA S4 (1999-2001) and KORA F4 (2006–2008) studies	
Annual DM onset probability, per person-year, in PreDM group	0,0105 CI 95% [0,008529; 0,01283]		
Annual DM onset probability, per person-year, in bout groups of NoDM and PreDM	0,0051 CI 95% [0,00432; 0,00598]		
The progression of complications			
Probability of additional LEA in sub-module of neuropathy	28%	Skoutas, D., Papanas, N., Georgiadis, G. S., Zervas, V., Manes, C., Maltezos, E., & Lazarides, M. K., "Risk factors for ipsilateral reamputation in patients with diabetic foot lesions," *Int. J. Low. Extrem. Wounds*, vol. 8, no. 2, pp. 69–74, 2009.	
Probability of death from LEA in sub-module of neuropathy	31% CI 95% [25; 36]	Icks, A., Scheer, M., Morbach, S., Genz, J., Haastert, B., Giani, G., Glaeske, G., Hoffmann, F., "Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation," *Diabetes Care*, vol. 34, no. 6, pp. 1350–1354, 2011.	
Stroke to death transition probability Immediate (0-6 months) in stroke sub-module	0,08520	Icks, A., Claessen, H., Kvitkina, T., Narres, M., Weingärtner, M., Schwab, S., Kolominsky-Rabas, P.L., "Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register," *PLoS One*, vol. 12, no. 11, pp.	

		1–15, Aug. 2017.	
Stroke to death transition probability (one-year)	0,05490	Icks, A., Claessen, H., Kvitkina, T., Narres, M., Weingärtner, M., Schwab, S., Kolominsky-Rabas, P.L., “Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register,” *PLoS One*, vol. 12, no. 11, pp. 1–15, Aug. 2017.	
Probability of diabetic foot ulcer in sub-module of neuropathy in stroke sub-module	0,87% CI 95% [0,53;1,41]	Rasmussen, A., Almdal, T., Anker Nielsen, A., Nielsen, K.E., Jørgensen, M.E., Hangaard, S., Siersma, V., Holstein, P. E., “Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period 2001–2014,” *Diabetes Res. Clin. Pract.*, vol. 130, pp. 221-228, Aug 2017.	
Annual incidence for standard glycemic control (% in 1 year)	0,54%	Dennis JM, Henley WE, McGovern AP, Farmer AJ, Sattar N, Holman RR, Pearson, E. R., Hattersley, A. T., Shields, B. M., Jones, A. G., "Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010–2017,” *Diabetes Obes. Metab.,* vol. 21, pp. 1576–1584, 2019.	
Relative risk of severe hypoglycemia	2,39	Hemmingsen, B., Lund, S.S., Gluud, C., Vaag, A., Almdal, T., Hemmingsen, C., Wetterslev, J., “Intensive glycaemic control for patients with type 2 diabetes: Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials,” *BMJ (online)*, vol. 343, p. 1136, 2011.	
Percent of hypoglycemia events requiring medical assistance	14 %	Schloot, N.C., Haupt, A., Schütt, M., Badenhoop, K., Laimer, M., Nicolay, C., Reaney, M, Fink, K.,	

		Holl, R. W., "Risk of severe hypoglycemia in sulfonylurea-treated patients from diabetes centers in Germany/Austria: How big is the problem? Which patients are at risk?," *Diabetes Metab. Res. Rev.*, vol. 32, no. 3, pp. 316–324, 2016.	
QOL decrement for hypoglycemia requiring medical assistance	0,012 CI 95% [0,020; 0,005]	Beaudet, A., Clegg, J., Thuresson, P.-O.O., Lloyd, A., McEwan, P., "Review of utility values for economic modeling in type 2 diabetes," *Value Health*, vol. 17, no. 4, pp. 462-470, 2014.	
QOL decrement for hypoglycemia not requiring medical assistance	0,004 CI 95% [0,031;0,001]	Currie, C.J., Morgan, C.L., Poole, C.D., Sharplin, P., Lammert, M., McEwan, P., "Multivariate models of health- related utility and the fear of hypoglycaemia in people with diabetes," *Curr. Med. Res. Opin.*, vol. 22, no. 8, pp. 1523-1534, 2006.	
Annual Mortality rate of Hypoglycemia, in %	1,14 %	Bonds, D.E., Miller, M.E., Bergenstal, R.M., Buse, J.B., Byington, R.P., Cutler, J.A., Dudl, R. J, Ismail-Beigi, F., Kimel, A.R., Hoogwerf, B., Horowitz, K. R., Savage, P. J.,Seaquist, E. R., Simmons, D. L., Sivitz, W. I., Speril-Hillen, J. M., Sweeney, M.E., "The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: Retrospective epidemiological analysis of the ACCORD study," *BMJ (online)*, vol. 340, p. 137, 2010.	
Initial Distribution of Individuals to Disease States			
Nephropathy sub-module: Normal	90,5 %	Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes	
Nephropathy sub-module: Microalbuminuria	9,5 %		

Nephropathy sub-module: Nephropathy	0 %	in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014.	
Nephropathy sub-module: ESRD	0 %		
Neuropathy sub-module: Normal	94,30 %	Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014.	
Neuropathy sub-module: Peripheral Neuropathy	5,70 %		
Neuropathy sub-module: LEA	0 %		
Retinopathy sub-module: Normal	96,40 %	Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014.	
Retinopathy sub-module: Photocoagulation	3,60 %		
Retinopathy sub-module: Blind	0 %		
Coronary Heart Disease sub-module: Normal	80,52 %	1. Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014. 2. Christensen, D.H., Nicolaisen, S.K., Berencsi, K., Beck-Nielsen, H., Rungby, J., Friborg, S., Brandslund, I., Christiansen, J. S., Vaal, A., Sørensen, H.T., Nielsen, J.S., Thomsen, R.W., "Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: A cohort profile," *BMJ Open*, vol. 8, no. 4, 2018.	

Coronary Heart Disease sub-module: Angina	8,58 %	Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014.	
Coronary Heart Disease sub-module: History of CA/MI	6,90 %		
Coronary Heart Disease sub-module: Congestive Heart Failure	4 %	Christensen, D.H., Nicolaisen, S.K., Berencsi, K., Beck-Nielsen, H., Rungby, J., Friborg, S., Brandslund, I., Christiansen, J. S., Vaal, A., Sørensen, H.T., Nielsen, J.S., Thomsen, R.W., "Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: A cohort profile," *BMJ Open*, vol. 8, no. 4, 2018.	
Stroke sub-module: Normal	94,70 %	Kostev, K., Jockwig, A., Hallwachs, A., Rathmann, W., "Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK," *Prim. Care Diabetes*, vol. 8, no. 3, pp. 250-255, 2014.	
Stroke sub-module: Stroke	5,30 %		
Economic parameters			
Consumer Price Index (CPI) and CPI Medical component	See Table 5	Consumer Price Index of All Items in Germany (DEUCPIALLMINMEI) | FRED | St. Louis Fed [Internet]. [cited 2020 Apr 10]. Available from: https://fred.stlouisfed.org/series/DEUCPIALLMINMEI Consumer Price Index: Health (COICOP 06): Total: Total for Germany (DEUCP060000IXOBM) | FRED | St. Louis Fed [Internet]. [cited 2020 Apr 10]. Available from: https://fred.stlouisfed.org/series/DEUCP060000IXOBM	

Discount Rate of Costs	3,5 (CI: 1,5-6,5)	NICE. National Institute of Clinical Excellence (NICE). Guide to the Technology Appraisal Process.	Costs and utilities were discounted by an annual discount rate of 3.5% per year, which is the rate recommended by NICE.
Discount Rate of Life Years and QALYs	3,5 (CI: 1,5-6,5)		
Year of input costs (Hermann model)	2015	Kähm, K., Laxy, M., Schneider, U., Rogowski, W. H., Lhachimi, S. K., Holle, R., “Health Care Costs Associated With Incident Complications in Patients With Type 2 Diabetes in Germany,” *Diabetes Care*, vol. 41, no. 5, pp. 971-978, 2018.	
The Herman Multiplicative Model parameters: the one-year acute event costs, regression model multipliers, and base-costs	See Table 6, Table 7, Table 8	Kähm, K., Laxy, M., Schneider, U., Rogowski, W. H., Lhachimi, S. K., Holle, R., “Health Care Costs Associated With Incident Complications in Patients With Type 2 Diabetes in Germany,” *Diabetes Care*, vol. 41, no. 5, pp. 971-978, 2018.	
Herman Additive QOL Model parameters: the equation’s intercepts and coefficients	See Table 9	Laxy, M., Backer, J., Kähm, K., Holle, R., Peters, A., Thorand, B., Schwettmann, L., Karl, M.F., “Diabetes, related complications, and quality of life: A German reference value set based on a population-based survey,” 2020.	In the study, health-related quality of life (HRQL) was assessed by the index-based questionnaire EQ-5D-5L and the EuroQol-visual analogue scale (EQ-VAS).
Intervention parameters			
The hazard rate of hypertension in normoglycemic group (NoDM) of DPP like intervention in placebo group	0,022246	Diederichs, C., Neuhauser, H., “The incidence of hypertension and its risk factors in the German adult population: Results from the German National Health Interview and Examination Survey1998 and the German Health Interview and Examination Survey forAdults 2008-2011,” *J. Hypertens*, vol. 35, no. 2, pp. 250-258, 2017.	
The hazard rate of hypertension in IGT group (PreDM) of DPP like intervention in placebo group	0,022246		
The distribution of patients newly diagnosed with NoDM and PreDM in DPP like intervention:	64,8 %	The estimates were derived in the analysis of the baseline KORA S4 (1999-2001)	

Group NoDM			
Group PreDM	29,5 %		
Group DM	5,74 %		
Costs for fasting glucose testing	14.78 €/unit	Icks, A., Haastert, B., John, J., Lowel, H., Holle, R., Giani, G., Rathmann, W., "Cost-Effectiveness Analysis of Different Screening Procedures for Type 2 Diabetes," *Diabetes Care*, vol. 27, no. 9, pp. 2120-2128, 2004.	
Costs for OGTT	16.34 €/unit		
Costs for HbA1c	16.00 €/unit		
Average labor costs per hour of an employee	29.19 €		
Average labor costs per hour of the civil service	5.37 €		
Health insurance: overall costs OGTT	503,779 €		
Health insurance: overall costs OGTT + HbA1c	2,203,502 €		
Society: overall costs fasting glucose + OGTT	1,115,142 €		
Society: overall costs HbA1c + OGTT	3,264,646 €		
Costs per detected case	499 €		
Average index fees for 39 practices	522.72 €	Gandjour, A., Kleinschmit, F., Lauterbach, K.W., "European comparison of costs and quality in the prevention of secondary complications in Type 2 diabetes mellitus (2000-2001)," *Diabet Med [Internet]*, vol. 19, no. 7, pp. 564-601, Jul. 2002.	
Average country-specific unit price	381.27 €		
Costs for one practice including index fees and country-specific unit price	23.17 €		

Total costs per subject	31.77 €	Icks, A., Haastert, B., John, J., Lowel, H., Holle, R., Giani, G., Rathmann, W., "Cost-Effectiveness Analysis of Different Screening Procedures for Type 2 Diabetes," *Diabetes Care*, vol. 27, no. 9, pp. 2120-2128, 2004.	
Diabetes sensitivity: default value	0.874	Rathmann, W., Kowall, B., Tamayo, T., Giani, G., Holle, R., Thorand, B., Heier, M., Huth, C., Meisinger, C., "Hemoglobin A1c and glucose criteria identify different subjects as having type 2 diabetes in middle-aged and older populations: The KORA S4/F4 Study," *Ann. Med. [Internet]*, vol. 44, no. 2, pp. 170-177, Mar. 22 2012.	
Diabetes specificity: default value	0.721		
Pre-diabetes sensitivity: default value	0.27		
Pre-diabetes specificity: default value	0.93		
Diabetes sensitivity: German setting	0.21		
Diabetes specificity: German setting	0.987		
Pre-diabetes sensitivity: German setting	0.76		
Pre-diabetes specificity: German setting	0.94		

Table 1 Prevalence of DM given by age and sex groups in the KORA sample.

Sex	Age group, years	DM, number of cases	Total population	Prevalence DM, %
Female	25-34	3	430	0.70
	35-44	9	457	1.97
	45-54	16	451	3.55
	55-64	39	430	9.07
	65-74	41	364	11.26
Male	25-34	2	400	0.50
	35-44	4	408	0.98
	45-54	12	413	2.91
	55-64	46	436	10.55
	65-74	68	390	17.44

Table 2 Mean systolic and diastolic blood pressure by age- and hypertension groups

Hypertension group	Age group, years	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg
Normal	0-24	118	73
	25-34	117.6	75.6
	35-44	121.6	80.0
	45-54	130.1	84.6
	55-64	133.2	81.0
	65-74	140.4	80
	75-84	140	80
	85-94	142	72
Above Normal	0-24	160	99
	25-34	160	99

	35-44	160	99
	45-54	168	93
	55-64	168	93
	65-74	164	81
	75-84	174	73
	85-94	172	78

Table 3 Total mortality rates in Germany.

Sex	Min age	Max age	White, no. of individuals	African Americans, no. of individuals	Hispanic, no. of individuals	Asians, no. of individuals	Native Americans, no. of individuals
Female	0	0	36328	0	0	0	0
Female	1	4	2011	0	0	0	0
Female	5	9	909	0	0	0	0
Female	10	14	1021	0	0	0	0
Female	15	19	2332	0	0	0	0
Female	20	24	2666	0	0	0	0
Female	25	29	2856	0	0	0	0
Female	30	34	3878	0	0	0	0
Female	35	39	6488	0	0	0	0
Female	40	44	11207	0	0	0	0
Female	45	49	19254	0	0	0	0
Female	50	54	29659	0	0	0	0
Female	55	59	44022	0	0	0	0
Female	60	64	64961	0	0	0	0
Female	65	69	102227	0	0	0	0
Female	70	74	179874	0	0	0	0
Female	75	79	334226	0	0	0	0
Female	80	84	633893	0	0	0	0

Female	85	89	1200703	0	0	0	0
Female	90	93	2130171	0	0	0	0
Female	94	94	1000000	1000000	1000000	1000000	1000000
Male	0	0	44839	0	0	0	0
Male	1	4	2362	0	0	0	0
Male	5	9	1188	0	0	0	0
Male	10	14	137	0	0	0	0
Male	15	19	5266	0	0	0	0
Male	20	24	7571	0	0	0	0
Male	25	29	7321	0	0	0	0
Male	30	34	8567	0	0	0	0
Male	35	39	12601	0	0	0	0
Male	40	44	21545	0	0	0	0
Male	45	49	36735	0	0	0	0
Male	50	54	5776	0	0	0	0
Male	55	59	8861	0	0	0	0
Male	60	64	136322	0	0	0	0
Male	65	69	213988	0	0	0	0
Male	70	74	347128	0	0	0	0
Male	75	79	566779	0	0	0	0
Male	80	84	946433	0	0	0	0
Male	85	89	1606668	0	0	0	0
Male	90	93	2641876	0	0	0	0
Male	94	94	1000000	1000000	1000000	1000000	1000000

Table 4 CVD mortality rates in Germany

Sex	min age	max age	mortality rate White	mortality rate African Americans	mortality rate Hispanic	mortality rate Asians	mortality rate Native Americans
Female	0	0	6	0	0	0	0

Female	1	14	2	0	0	0	0
Female	15	19	4	0	0	0	0
Female	20	24	2	0	0	0	0
Female	25	29	1	0	0	0	0
Female	30	34	16	0	0	0	0
Female	35	39	19	0	0	0	0
Female	40	44	58	0	0	0	0
Female	45	49	104	0	0	0	0
Female	50	54	189	0	0	0	0
Female	55	59	338	0	0	0	0
Female	60	64	62	0	0	0	0
Female	65	69	1085	0	0	0	0
Female	70	74	213	0	0	0	0
Female	75	79	469	0	0	0	0
Female	80	84	11294	0	0	0	0
Female	85	89	25056	0	0	0	0
Female	90	93	55147	0	0	0	0
Female	94	94	55147	0	0	0	0
Male	0	0	11	0	0	0	0
Male	1	14	0	0	0	0	0
Male	15	19	3	0	0	0	0
Male	20	24	8	0	0	0	0
Male	25	29	12	0	0	0	0
Male	30	34	29	0	0	0	0
Male	35	39	69	0	0	0	0
Male	40	44	148	0	0	0	0
Male	45	49	326	0	0	0	0
Male	50	54	639	0	0	0	0
Male	55	59	1179	0	0	0	0
Male	60	64	1982	0	0	0	0
Male	65	69	3143	0	0	0	0
Male	70	74	5196	0	0	0	0

Male	75	79	9194	0	0	0	0
Male	80	84	18628	0	0	0	0
Male	85	89	34709	0	0	0	0
Male	90	93	66202	0	0	0	0
Male	94	94	66202	0	0	0	0

Table 5 Consumer Price Index (CPI) and CPI Medical component in the USA and Germany given by the Federal Reserve Bank of St. Louis.

	USA		Germany	
Year	**CPI**	**CPI Medical component**	**CPI**	**CPI Medical component**
1990	130.66	162.81	62.94	/
1991	136.17	177.02	65.49	60.27
1992	140.31	190.06	68.80	62.45
1993	144.48	201.40	71.88	64.17
1994	148.23	211.03	73.82	66.31
1995	152.38	220.45	75.08	66.96
1996	156.86	228.27	76.17	68.15
1997	160.53	234.59	77.64	72.86
1998	163.01	242.13	78.35	76.65
1999	166.58	250.56	78.81	74.14
2000	172.19	260.75	79.94	74.30
2001	177.04	272.77	81.53	75.27
2002	179.87	285.63	82.69	75.80
2003	184.00	297.06	83.54	76.04
2004	188.91	310.14	84.93	90.68
2005	195.27	323.23	86.25	92.29
2006	201.56	336.19	87.61	92.71
2007	207.34	351.06	89.62	93.86
2008	215.25	364.07	91.98	95.44
2009	214.56	375.61	92.27	96.38
2010	218.08	388.42	93.28	97.17

2011	224.92	400.24	95.22	97.84
2012	229.59	414.92	97.13	100.24
2013	232.95	425.13	98.59	96.54
2014	236.72	435.31	99.49	98.48
2015	237.00	446.76	100.00	100.00
2016	239.99	463.69	100.49	101.12
2017	245.12	475.32	102.01	102.49
2018	251.10	484.71	103.78	103.43
2019	255.65	498.42	105.28	104.47
2020	260.21 /	523.55	106.02	105.19

Table 6 German specific Herman one-year acute event costs

Acute event	**Costs, in Euro**
Acute myocardial infarction	9,841
Congestive heart failure	5,862
Stroke	15,619
Amputation	21,625
End Stage Renal Disease (ESRD)	38,465
Costs of normal death	5,589

Table 7 German specific multipliers associated with individual-specific factors used in the Herman Multiplicative Model for Individuals with diabetes, pre-diabetes and with normoglycemia.

Factor	**Cost multipliers**		
	DM	**PreDM**	**NoDM**
Female	1.048234	1.065867	1.103825
White	1	1	1
African American	1	1	1
Hispanic	1	1	1
Asian	1	1	1

Native American	1	1	1
BMI excess over 30 kg/m2	1	1	1
Oral anti-diabetic agents	1	1	1
Insulin	1	1	1
Microalbuminuria	1	1	1
Nephropathy	1.345251	1.471472	1.743169
ESRD with dialysis	6.840491	8.975733	13.57195
History of stroke	1.537339	1.733786	2.156648
Angina	0.990692	0.987289	0.979964
History of CA/MI	1.044003	1.06009	1.094718
Congestive heart failure	1.45018	1.614762	1.969035
Peripheral vascular disease	1	1	1
Hypertension (treated)	1	1	1

Table 8 German specific Herman base-costs

Herman baseline cost for…	**Costs, in Euro**
Diabetes	4,727.00
Undiagnosed diabetes	4,727.00
Diabetes remission	2,196.00
Pre-diabetes	3,461.50
Undiagnosed pre-diabetes	3,461.50
NGT	2,196.00

Table 9 German specific Herman additive QOL coefficients

Factor	**Coefficient**
Diabetes Intercept: onset to diagnosis	0.7000
Diabetes Intercept: early diagnosis to clinical diagnosis	0.7000
Diabetes Intercept: after clinical diagnosis	0.7000

IGT Intercept	0.7173
NGT Intercept	0.7220
Female	-0.0270
Hypertension	-0.0010
Blind	-0.1000
Nephropathy	-0.0640
End Stage Renal Disease (ESRD)	-0.0640
Peripheral Neuropathy	-0.0920
Foot Ulcer	-0.0370
Lower Extremity Amputation	-0.0370
History of CA/MI	-0.0140
Congestive heart failure	-0.0800
Stroke	-0.0690
BMI >= 30.0	-0.0400

Internal validation

As recommended in the principles of good practice for modelling in health-care evaluation (1), we also validate the new German-specific setting of the CDC-RTI Diabetes Model in parts where we have introduced changes. For the validation, we input baseline model parameters from studies that were used to adapt the model (internal validation) and those that were not used to adapt the model (external validation). We then run the model and compare the overall outcomes in the model to those reported by the validation studies.

In the internal validation, we simulate the course of disease in the adapted setting and compare the simulation results with those in the original data source used to estimate parameters under the interest. We validate the adapted model using the KORA data set that was the source of an initial population structure and incidence of diabetes. We compare the cumulative incidence of T2DM between KORA S4 (1999-2001) and KORA F4 (2006–2008) studies with the simulated cumulative incidence prognoses in 8 and 9 years from the start of the simulation. The cumulative incidence of T2DM in KORA is estimated at 4.24% in follow-up for a median of 8.8 years in the complete cohort after the basic examination (validated data). The simulated cumulative incidence of T2DM is recoded as 3.86% in 8 years and 4.30% in 9 years of simulation that can be transformed to 4.21% in 8.8 years follow-up and shows an agreement with observed results.

External validation

In the original CDC-RTI Diabetes Model all-cause mortality outcome was externally validated (2) against two studies: Gu et al. analyzed representative cohorts of subjects with and without diabetes derived from the First National Health and Nutrition Examination Survey (NHANES I) conducted between 1971 and 1975 (3) and Sakaki et al. examine a 15 year follow-up study of diabetic patient performed in Osaka, Japan (4). In both all-cause mortality (deaths per 1,000 person years) was validated. The results were satisfying: the model accurately predicts the total-cause mortality for the Japanese diabetes population in Sasaki et al. (89) and the American diabetes population in Gu, Cowie, and Harris (3). Despite the difference in country, the model is within 10 percent of the published estimate for Japan.

We externally validate the adapted CDC-RTI Diabetes Model. We validate the all cause cumulative mortality in the simulation with the cumulative mortality between KORA S4 (1999-2001) and KORA F4 (2006–2008) studies in persons with NGT and IGT. We have not used the mortality in the KORA for adapting the original model, that is why the validation by mortality outcome can be treated as external. After running the model for the simulated cohort, we compared the model outcomes (cumulative all-cause mortality) with the outcomes described in the comparison study. The cumulative mortality among those without diabetes at the baseline was 5.01% in the KORA study during average 8.8 years of follow-up. In the simulation, the all-cause mortality at 8 years was 7.08% and at 9 years 8.14% that comprises 7.93% in 8.8 years.

Also, we compare the simulated cumulative mortality of CHD and stroke with the empirical observations in the KORA data. In the data source, CHD mortality was defined by ICD-9 codes 410-414 and 798, and stroke mortality was defined ICD 9 codes 430, 431, 433, 434, 436. The ICD-9 codes and their ICD-10 analogues as well as the name of diagnosis can be found in Table 10. The cumulative CHD mortality was estimated as 0.91% and stroke mortality was 0.33% in the KORA during average 8.8 years of follow-up. The simulation results are given in Table 11.

Table 10 The ICD codes for CVD events

ICD-9 code	**ICD-10 code**	**Name of diagnosis**
410	I2109	Acute myocardial infarction
411	I241, I200, I240, I248	Other acute and subacute forms of ischemic heart disease
412	I252	Old myocardial infarction
413	I201, I208, I209	Angina pectoris
414	I25.89, I25.9	Other forms of chronic ischemic heart disease
798	R99	Sudden death cause unknown
430	I609	Subarachnoid hemorrhage
431	I619	Intracerebral hemorrhage
433	I65	Occlusion and stenosis of precerebral arteries
434	I66	Occlusion of cerebral arteries
436	I6789	Acute, but ill-defined, cerebrovascular disease

Table 11 Cumulative mortality in the simulation results and in the observational study

Cumulative Mortality, %	**In the KORA study**	**In the simulation**		
	8.8 years	**8 years**	**9 years**	**8.8 years**

All-cause	5.01%	7.08%	8.14%	7.93%
CHD	0.91%	2.01%	2.31%	2.25%
Stroke	0.33%	0.28%	0.32%	0.312%

In the CDC-RTI Diabetes Model, CHD and stroke diabetes complications are treated as separate disease components using several risk equation engines. One of them is the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, presented in UKPDS 56 and UKPDS 60 (1987). Recent studies have suggested that UKPDS-based risk predictions consistently overestimate the risk of CVD and mortality. Moreover, it was shown that The UKPDS significantly over-predicted mortality and CV mortality in patients with T2DM from the KORA cohort by 25% and 28%, respectively.

American College of Cardiology/American Heart Association (ACC/AHA) recently developed risk equations to estimate the 10-year atherosclerotic cardiovascular disease (ASCVD) risk to guide statin initiation in non-Hispanic black and non- Hispanic white men and women aged 40 to 79 (5). The ACC/AHA risk equations have been assessed for calibration and discrimination by at least two studies: Muntner et al. (6) using data from the REGARDS study, and DeFilippis et al. (7) using data from the MESA study. The. The ACC/AHA equations use the most recent 10-year data from the Coronary Artery Risk Development in Young Adults (CARDIA), Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), and Framingham studies to predict macrovascular outcomes.

In the simulation, we used this ACC/AHA CVD Risk Equation. Unfortunately, these risk equations were not validated and/or calibrated for the German population. Our results reveal partly agreement with observed results showing higher mortality in our simulation, particularly from CHD, than in the KORA data.

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