Endocrine (2019) 63:259–269
https://doi.org/10.1007/s12020-018-1727-9

ORIGINAL ARTICLE

Cost-effectiveness of a primary care multidisciplinary Risk Assessment and Management Program for patients with diabetes mellitus (RAMP-DM) over lifetime

Fangfang Jiao[1] · Eric Yuk Fai Wan[1] · Colman Siu Cheung Fung[1] · Anca Ka Chun Chan[1] · Sarah Morag McGhee[2] · Ruby Lai Ping Kwok[3] · Cindy Lo Kuen Lam[1]

Received: 6 April 2018 / Accepted: 14 August 2018 / Published online: 28 August 2018

Abstract

Purpose The multidisciplinary Risk Assessment and Management Program for patients with diabetes mellitus (RAMP-DM) was found to be cost-saving in comparison with usual primary care over 5 years' follow-up. This study aimed to estimate the cost-effectiveness of RAMP-DM over lifetime.

Methods We built a Discrete Event Simulation model to evaluate the cost-effectiveness of RAMP-DM over lifespan from public health service provider's perspective. Transition probabilities among disease states were extrapolated from a cohort of 17,140 propensity score matched participants in RAMP-DM and those under usual primary care over 5-year's follow-up. The mortality of patients with specific DM-related complications was estimated from a cohort of 206,238 patients with diabetes. Health preference and direct medical costs of DM patients referred to our previous studies among Chinese DM patients.

Results RAMP-DM individuals gained 0.745 QALYs and cost US$1404 less than those under usual care. The probabilistic sensitivity analysis found that RAMP-DM had 86.0% chance of being cost-saving compared to usual care under the assumptions and estimates used in the model. The probability of RAMP-DM being cost-effective compared to usual care would be over 99%, when the willingness to pay threshold is HK$20,000 (US$ 2564) or higher.

Conclusion RAMP-DM added to usual primary care was cost-saving in managing people with diabetes over lifetime. These findings support the integration of RAMP-DM as part of routine primary care for all patients with diabetes.

Keywords Cost-effectiveness · Diabetes mellitus · Multidisciplinary · Risk assessment and management · Primary care

Introduction

There are 415 million people with diabetes mellitus (DM) all over the world by 2015, and the number is estimated to climb to 642 million by 2040 [1]. Care of people with diabetes takes a large percentage of the total health care budget all over the world. The percentages were 10% in the US [2], 2.5–6.5% in European countries [3], 6.4% in Hong Kong [4], and 12% globally [1]. In view of the rising prevalence and giant financial burden of DM, it is imperative to implement effective and inexpensive interventions to enable cost-effective management of DM patients.

In recent years, risk stratification-based management [5–7] was recommended by guidelines. Based on the stratification of patients' individual cardiovascular risks, personalized treatment module were prescribed. To implement risk stratification-based management, a multidisciplinary

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12020-018-1727-9) contains supplementary material, which is available to authorized users.

✉ Eric Yuk Fai Wan
yfwan@hku.hk

[1] Department of Family Medicine and Primary Care, The University of Hong Kong, 3/F., 161 Main Street, Ap Lei Chau Clinic, Ap Lei Chau, Hong Kong, Hong Kong

[2] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 5/F, William MW Mong Block, 21 Sassoon Road, Hong Kong, Hong Kong

[3] Primary and Community Services, Hospital Authority Head Office, Hong Kong Hospital Authority, Hospital Authority Building, 147B Argyle Street, Kowloon, Hong Kong, Hong Kong

team is required, including nurses, doctors, and allied health professionals. Accumulating evidence shows that multidisciplinary interventions can improve blood glucose control [8–11] and reduce complications in people with diabetes [12].

The Hong Kong Hospital Authority (HA), the main public health service provider, has launched the risk assessment and management program for patients with diabetes mellitus (RAMP-DM) in Hong Kong public general out-patient clinics (GOPCs) since August 2009 to enhance the care of DM patients in primary care setting. The details of the program have been reported [13]. In short, RAMP-DM patients were stratified into different risk levels based on Intake Assessment, which was a comprehensive risk assessment, including measurement of risk factors for cardiovascular and renal complications, eye and foot assessment. Structured management were provided to RAMP-DM participants according to different risk levels. People with diabetes under usual primary care continued to be managed by their primary care doctors without risk assessment and stratification. Previous studies found that, compared to usual primary care, RAMP-DM was effective in reducing both macrovascular and microvascular complications and mortality over 1-year, 3-year, and 5-year's intervention [14–17]. RAMP-DM was also found to be cost-saving in terms of lower complication and mortality rates and a net saving of US$7294 in medical costs per participant over 5 years' observation [18]. The long-term cost-effectiveness of RAMP-DM was unknown.

Several previous studies have investigated the long-term cost-effectiveness of multidisciplinary DM management programs. Gaede et al. (Steno-2 study) [19] found lower incidences of acute myocardial infarction (AMI) and stroke in the intervention group compared to usual care over 8 years, the results of which were used to develop age-adjusted coefficients for AMI and stroke transition probabilities (TPs) in a lifetime model. It was found the intervention was cost-effective with an incremental cost-effectiveness ratio (ICER) of €2538 (US$2835)/quality-adjusted life years (QALY) over lifetime. However, another study in the UK (ADDITION-UK study) found similar intervention did not significantly decrease the incidences of cardiovascular disease (CVD) events (hazard ratio 0.83, 95% CI (0.65–1.05)) over 5 years in screening detected DM patients [20]. In the lifetime simulation, the intervention costs £37,500 (US$48,638)/QALY, which was not cost-effective against the threshold of £30,000 (US$38,910) [21].

Several studies extrapolated 1–2 years' changes in clinical disease parameters, including HbA1c, blood pressure, and lipid profiles to lifetime cost-effectiveness evaluation. Two studies in the US estimated the long-term cost-effectiveness of a protocol driven, multifaceted electronic clinical decision support program [22] and a stratified patient-centered program [23], respectively. The ICER for these two interventions were US$3017/QALY and US $6443/QALY, respectively, which were both considered cost-effective against the benchmark of US$50,000/QALY in the US [24].

A Multifaceted Computerized Decision Support DM management program in the Netherlands extrapolated the effects of 1-year intervention to lifetime model and found the ICER was €38,243 (US$42,758) per QALY. The likelihood of cost-effectiveness was 30% given a willingness to pay threshold of €20,000 (US$22,361) [3]. Another quality improvement collaborative program in the Netherlands found that the multidisciplinary intervention was cost-effective with an ICER of €1937 ($2166)/QALY for men and €1751 (US$1958)/QALY for women [25]. Both studies in the Netherlands applied the differences in clinical disease parameters between the intervention and usual care groups over 1–2 years to the United Kingdom Prospective Diabetes Study (UKPDS) risk engines [26, 27].

Previous studies found inconsistent conclusions on the long-term cost-effectiveness of multidisciplinary DM management programs. Most of the studies extrapolated the long-term effectiveness of reduction in complications from short term changes in surrogate clinical outcomes of HbA1c, blood pressure, and lipid profiles, which might have led to the variation in the CEA results. There were few studies with sufficient period of follow-up to measure the indicator clinical outcomes DM-related complications and death for valid evaluation of the long-term cost-effectiveness of multidisciplinary DM management programs.

The aim of this study was to evaluate the cost-effectiveness of continuous RAMP-DM management in addition to usual primary care compared to usual primary care only in patients with DM over a lifetime from the health service provider's perspective in the Hong Kong.

Materials and methods

Intervention and comparators

The compared interventions in this study were usual primary care versus usual primary care supplemented by RAMP-DM. The RAMP-DM intervention was assumed to be maintained over the entire modeled simulation period.

The simulated population consisted of 10,000 DM patients in each group. The characteristics of patients simulated were those of the two cohorts of 17,140 DM subjects (8570 in RAMP-DM and usual care group, respectively) in the 5-year cost-effectiveness study of RAMP-DM study described previously [18]. The baseline age was 67 ± 12 years old, and 52% were female. All

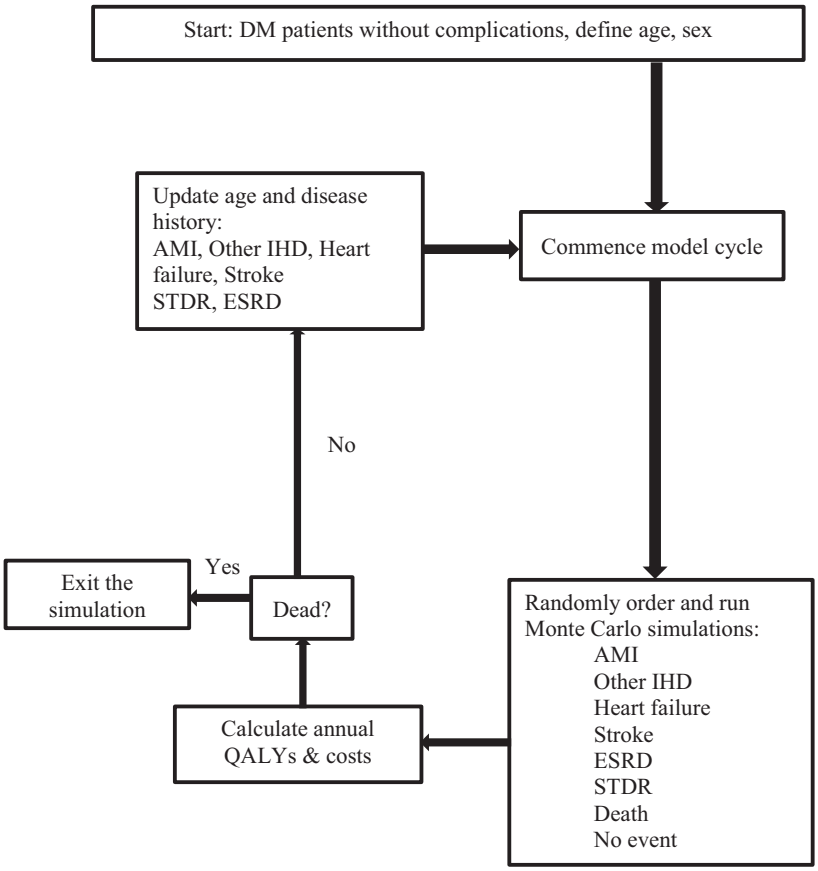

Fig. 1 Structure of the model

AMI, acute myocardial infarction; DM, diabetes mellitus; ESRD, end stage renal disease; IHD, ischemic heart disease; QALY, quality adjusted life year; STDR, Sight-threatening diabetic retinopathy.

patients were free of complications at entry to the model. Within the simulation, patients were assumed to remain in the same RAMP-DM intervention or usual care group for the entire period of the modeled disease progression (60 years or death).

Modeling approach

The modeling approach employed was a Discrete Event Simulation model to simulate the lifelong progression of people with DM from no complication along possible major diabetes-related complication paths to death. Six diabetes-related complications were included in the model, namely, AMI, other ischemic heart disease (IHD), heart failure, stroke, end stage renal disease (ESRD), and sight-threatening diabetic retinopathy (STDR), which are major contributors to reductions in quality of life, increased health service costs and mortality.

The model structure is shown in Fig. 1. At entry, individuals were free from any complications. The disease states transition was at 1-year interval. At the end of each year, each individual could develop one or more complications, die or stay without any complication. In this model, more than one complication was possible to happen in any year in the same subject, but the recurrence of the same complication was not allowed in the simulation.

This model applied Monte Carlo simulation to simulate the disease path at an individual level, which can keep track of the timing and types of different and multiple diabetic complications (i.e., disease states). To determine whether an individual would experience an event in any year, a random number was drawn from a uniform distribution from 0 to 1. If this number was smaller than the transition probability of the event, the subject would be assumed to have the event. The cost and utility scores for each subject in each disease state were calculated, as well as the cumulative quality-adjusted life years and lifetime health service costs. By comparing the between-group differences in average lifetime costs, life years (LYs) and quality-adjusted life years (QALYs), we calculated the incremental cost per LYs gained and cost per QALY gained for the intervention.

Transition probabilities

The probabilities of developing the six complications were derived from the findings of the cohort study on 17,140 patients with diabetes with 5-year follow-up described in previous study [18]. Since age and sex were found to be associated with different risks of DM complications [26–30], we investigated the effect of age on the six complications in each intervention, sex-specific groups among 17,140 patients with diabetes with 5-year follow-up. The hazard ratio of age was used to adjust the TPs over lifetime. Therefore, the TPs of complications were determined by the subject's age, sex, and treatment group. The details of deriving TPs are described in Supplementary Material 1.

Mortality

The mortality was estimated from 206,238 people with diabetes managed in the HA public primary care clinics from 1 August 2008 to 31 December 2013. Models were developed to estimate the individual mortality taking into consideration the subject's age, sex, and presence of complications (AMI, other IHD, heart failure, stroke, and ESRD). Mortality rates were estimated for 4 scenarios: the first group was those whose death occurred in a year when they had no previous diagnosis of any of the 6 complications (group 1); the second and third groups were event-year mortalities in subjects without previous complications (group 2) and with pre-existing complications (group 3); the fourth group was those who died in a non-event year but had previous complications (group 4). The details of the mortality models are described in Supplementary Material 2. It was assumed the mortality of subjects in RAMP-DM and usual care groups were the same if they had the same disease status and demographic characteristics.

Direct medical costs over a lifetime

The costs for individuals in the RAMP-DM group included the costs of delivering RAMP-DM and the usual health services costs for managing patients with diabetes. The costs of individuals in the usual care group included costs of usual health services only.

The first year RAMP-DM costs included the one-off set-up cost, administrative costs and the on-going cost, but only RAMP-DM on-going costs were included in subsequent years as described in our previous study [18]. It was found that the average RAMP-DM intervention cost per subject in the second year and the third year was about half of that in the first year, because all RAMP-DM subjects had RAMP-DM interventions in the first year but only about half of them had repeat RAMP-DM in any subsequent year. Thus the average costs of the on-going RAMP-DM program in subsequent years were assumed to be half of that in the first year in the model (Supplementary Table 1).

The usual health service costs of managing DM patient were estimated from a previous study on the costs of patients with diabetes in Hong Kong [31]. The details of calculating annual public and private direct medical costs are shown in Supplementary Material 3. We assumed that the costs of managing DM subjects were the same in both RAMP-DM and usual care groups if the subjects had the same disease states.

Health outcomes

The main health outcomes were life years (LYs) and QALYs. The health preference of DM patients were from a previous study in Hong Kong population [32]. As shown in Supplementary Table 2, the health preference (utility) for DM subjects without any complication was 0.883. Females were found to have a lower health preference (coefficient: −0.024, $P = 0.005$) than male. We did not differentiate the health preference by types of heart diseases. Additive decrements would be applied if the subject had multiple complications. Stroke, ESRD, heart disease, and STDR were associated with lower SF-6D health preference, with reductions of −0.042 (95% CI −0.072 to −0.012), -0.055 (95% CI −0.093 to −0.017), (−0.017, 95% CI −0.042 to 0.008) and −0.043 (95%CI −0.075 to −0.010), respectively. The QALYs were calculated as the health preference of the disease state multiplied by LY in which the subject stayed in the state. The impact inventory is provided in Supplementary Table 4.

Lifetime cost-effectiveness

The measure of cost-effectiveness of RAMP-DM was the incremental cost per QALY gained (ICER) compared to usual care. By comparing the between-group differences in average lifetime costs, LYs and QALYs, we calculated the incremental cost per LYs gained and cost per QALY gained for the intervention. The ICER was compared to commonly adopted willingness to pay (WTP) thresholds of (1) £20,000/QALY (HK$240,000, exchange rate at £1 to HK $12) recommended by The National Institute for Health and Care Excellence (NICE) [33]; (2) HK$297,462/QALY (annual per capita GDP in Hong Kong) [34] recommended by the World Health Organization [35, 36]; and (3) US $50,000/QALY (HK$390,000, exchange rate at US$1 to HK$7.8), which was commonly adopted in the US [24].

Data analysis

The model was used to simulate 10,000 DM patients in each of the two groups, respectively. The model was run 100

Table 1 One-way sensitivity analysis

Parameters	Base-case	Range for sensitivity analysis	RAMP-DM vs usual care	
			Range for incremental cost (USD)	Range for incremental QALY
Cost				
Cost of RAMP-DM in the first year (USD)	65	30–103	(−1519, −1289)	NA
Cost of RAMP-DM in subsequent years (USD)	30	14–47	(−1530, −1253)	NA
Effectiveness				
Male				
Hazard ratio of AMI for RAMP-DM	0.471	(0.364, 0.610)	(−1430, −1365)	(0.739, 0.752)
Hazard ratio of other IHD for RAMP-DM	0.341	(0.278, 0.417)	(−1460, −1323)	(0.738, 0.762)
Hazard ratio of heart failure for RAMP-DM	0.507	(0.395, 0.652)	(−1421, −1387)	(0.725, 0.763)
Hazard ratio of stroke for RAMP-DM	0.754	(0.611, 0.930)	(−1601, −1193)	(0.717, 0.775)
Hazard ratio of ESRD for RAMP-DM	0.528	(0.427, 0.653)	(−1436, −1380)	(0.716, 0.769)
Hazard ratio of STDR for RAMP-DM	0.566	(0.362, 0.885)	(−1425, −1374)	(0.734, 0.757)
Female				
Hazard ratio of AMI for RAMP-DM	0.492	(0.381, 0.635)	(−1421, −1376)	(0.732, 0.755)
Hazard ratio of other IHD for RAMP-DM	0.532	(0.437, 0.647)	(−1438, −1355)	(0.733, 0.768)
Hazard ratio of heart failure for RAMP-DM	0.399	(0.322, 0.495)	(−1445, −1356)	(0.718, 0.775)
Hazard ratio of stroke for RAMP-DM	0.562	(0.461, 0.686)	(−1607, −1211)	(0.719, 0.773)
Hazard ratio of ESRD for RAMP-DM	0.657	(0.534, 0.808)	(−1489, −1314)	(0.732, 0.755)
Hazard ratio of STDR for RAMP-DM	0.383	(0.211, 0.695)	(−1445, −1367)	(0.744, 0.745)
Health preference				
AMI	−0.017	(−0.042, 0.008)	NA	(0.745, 0.746)
Other IHD	−0.017	(−0.042, 0.008)	NA	(0.744, 0.745)
Heart failure	−0.017	(−0.042, 0.008)	NA	(0.741, 0.748)
Stroke	−0.042	(−0.072, −0.012)	NA	(0.742, 0.749)
ESRD	−0.055	(−0.093, −0.017)	NA	(0.743, 0.746)
STDR	−0.043	(−0.075, −0.010)	NA	(0.744, 0.745)

RAMP-DM Risk Management and Assessment Programme-diabetes mellitus, *AMI* acute myocardial infarction, *IHD* ischemic heart disease, *ESRD* end stage renal disease, *STDR* sight threatening diabetic retinopathy, *QALY* quality-adjusted life years

times for each individual in the cohort using first-order Monte Carlo simulation to calculate the mean and standard deviation of costs, LYs, and QALYs. Both the costs and the outcomes were discounted at an annual rate of 3.5% [33].

Sensitivity analysis

To test the robustness of the results, we conducted probability sensitivity analysis, scenario analysis, and one-way sensitivity analyses. The probability of RAMP-DM to be cost-effective under a certain WTP threshold over the 10,000 simulations was illustrated by the cost-effectiveness plane. We also presented the CE acceptability curve to illustrate the probability of RAMP-DM being cost-effective under different levels of WTP threshold.

In the scenario analysis, we assumed the effectiveness of the RAMP-DM intervention maintained for 5 years, 8 years, or 10 years, respectively. One-way sensitivity analysis was carried out by varying the program costs of RAMP-DM within the ranges of costs among seven clusters. To investigate the variation in the cost-effectiveness results with the variations in the effectiveness of RAMP-DM, we applied 95% CI of the hazard ratios between RAMP-DM and the usual care groups on the six complications observed in previous study [18] to adjust the TPs in the RAMP-DM group against usual care group in the one-way sensitivity

Table 2 Cost-effectiveness of RAMP-DM versus usual care in terms of LYs and QALYs from the health service provider's perspective

	Cost (USD)			LY			Cost/LY (USD)	Incremental cost (USD)	Incremental LY	ICER (USD per LY)
	(a)			(b)			(a) / (b)	(d)	(e)	(d) / (e)
	Mean	SD	95% CI	Mean	SD	95% CI				
No discount on cost or effectiveness										
RAMP-DM	33,119	906	(31,425, 35,116)	11.622	0.275	(11.133, 12.145)	2850	−2691	1.267	NA
Usual care	35,810	1607	(32,788, 39,566)	10.355	0.287	(9.769, 10.949)	3458			
Only cost discounted at 3.5% per year										
RAMP-DM	23,267	524	(22,341, 24,374)	11.622	0.275	(11.133, 12.145)	2002	−1404	1.267	NA
Usual care	24,671	863	(23,054, 26,868)	10.355	0.287	(9.769, 10.949)	2383			
Cost and effectiveness discounted at 3.5% per year										
RAMP-DM	23,267	524	(22,341, 24,374)	8.616	0.166	(8.306, 8.911)	2700	−1404	0.807	NA
Usual care	24,671	863	(23,054, 26,868)	7.809	0.174	(7.473, 8.201)	3159			

	Cost (USD)			QALY			Cost/QALY (USD)	Incremental cost (USD)	Incremental QALY	ICER (USD per QALY)
	(a)			(b)			(a) / (b)	(d)	(e)	(d) / (e)
	Mean	SD	95% CI	Mean	SD	95% CI				
No discount on cost or effectiveness										
RAMP-DM	33,119	906	(31,425,35,116)	10.032	0.246	(9.532,10.644)	3,301	-2,691	1.166	NA
Usual care	35,810	1,607	(32,788,39,566)	8.866	0.249	(8.488,9.430)	4,039			
Only cost discounted at 3.5% per year										
RAMP-DM	23,267	524	(22,341,24,374)	10.032	0.246	(9.532,10.644)	2,319	−1,404	1.166	NA
Usual care	24,671	863	(23,054,26,868)	8.866	0.249	(8.488,9.430)	2,783			
Cost and effectiveness discounted at 3.5 % per year										
RAMP-DM	23,267	524	(22,341,24,374)	7.449	0.246	(7.151,7.826)	3,124	−1,404	0.745	NA
Usual care	24,671	863	(23,054,26,868)	6.704	0.249	(6.471,7.063)	3,680			

RAMP-DM Risk Management and Assessment Programme-diabetes mellitus, *QALY* quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *SD* standard derivation, *CI* confidence interval, *NA* not applicable

RAMP-DM Risk Management and Assessment Programme-diabetes mellitus, *LY* life years, *ICER* incremental cost-effectiveness ratio, *SD* standard derivation, *CI* confidence interval, *NA* not applicable

Table 3 Scenario sensitivity adnalysis from the health service provider's perspective

	Cost (USD) (a)	QALY (b)	Cost/QALY (USD) (a) / (b)	Incremental cost (USD) (d)	Incremental QALY (e)	ICER (USD per QALY) (d) / (e)
The effectiveness of RAMP-DM maintained for 5 years						
RAMP-DM	24,110 ± 721	7.116 ± 0.154	3388	−561	0.412	NA
Control	24,671 ± 863	6.704 ± 0.160	3680			
The effectiveness of RAMP-DM maintained for 8 years						
RAMP-DM	23,895 ± 671	7.229 ± 0.153	3305	−776	0.525	NA
Control	24,671 ± 863	6.704 ± 0.160	3680			
The effectiveness of RAMP-DM maintained for 10 years						
RAMP-DM	23,774 ± 617	7.286 ± 0.150	3263	−897	0.582	NA
Control	24,671 ± 863	6.704 ± 0.160	3680			

Data were expressed as mean ± SD. Both cost and QALYs were discounted at 3.5% per year

RAMP-DM Risk Management and Assessment Programme-diabetes mellitus, *QALY* quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *NA* not applicable

analysis (Table 1). The parameters used for probability sensitivity analysis included programme costs of RAMP-DM variation among 7 clusters, HRs associated with complications found in the cohort study, multipliers of public and private direct medical costs and utility scores for each complication as listed in Table 1. We applied the uniform distribution for programme costs of RAMP-DM, the log normal distribution for HRs and multipliers of costs and the normal distribution for utility scores.

Model validation

External validity of the CEA model was tested by comparing the modeled life expectancy to life expectancy of DM patients reported in the literature. A study including 820,900 subjects in 97 prospective studies (including 4 studies in Asia) [37], estimated that men with DM at 40, 50, and 60 years old but without vascular diseases had a loss of 6.3, 5.8, and 4.5 years, respectively, compared to people without DM. For women, the life loss associated with DM subjects at the age of 40, 50, and 60 years old were 6.8, 6.4, and 5.4 years, respectively. The subjects in the lifetime simulation in our study were 67 years old at entry, with 9 years duration of DM on average [18], Therefore, 5 years of life loss was expected compared to people without DM, assuming the life expectancy of people without DM was the same as that of the general population, which was 83 in Hong Kong [38]. Therefore, the model is assumed valid if the 95% CI of the simulated life expectancy covered 78.

Model assumptions

Assumptions on the model structures and parameters were listed in Supplementary Table 3. Impact inventory was listed in Supplementary Table 4.

The model and analysis were conducted using TreeAge Pro 2017, R1.

Results

Model validation

The simulated LY gains in the RAMP-DM and usual care groups was 11.62 (95% CI: 11.13–12.15) and 10.36 (95% CI: 9.77–10.95) years (Table 2) from the age of 67 when the subjects entered the model. This translated to a life expectancy of 78.62 (95% CI: 77.13–79.15) and 77.36 (95% CI: 76.77–77.95) for RAMP-DM and usual care DM patients, respectively. The simulated life expectancy of both groups covered the life expectancy validation standard of 78 years old.

Cost-effectiveness of RAMP-DM

Table 2 presents the results of the base case analysis of cost-effectiveness of RAMP-DM in comparison to usual care groups in terms of incremental cost per LY and incremental cost per QALY. When both cost and effectiveness were discounted at 3.5% every year, subjects in the RAMP-DM group and usual care group cost US$2700 and US$3159 per LY, and cost US$3124 and US$3680 per QALY, respectively. The cost per LY in the usual care group was more expensive than that of the RAMP-DM group, which was most likely due to the higher incidences of complications in the usual care group. The RAMP-DM group gained 1.267 LYs (undiscounted) and 1.166 QALYs (undiscounted) per subject over a lifetime. The RAMP-DM intervention was cost-saving in comparison to usual care. RAMP-DM saved direct medical cost of US$1404 (undiscounted) or US$1404 (discounted) per subject over a lifetime.

Sensitivity analysis

Supplementary Figure 1 demonstrates the probability sensitivity analysis by the cost-effectiveness plane under the base case with both cost and effectiveness discounted at 3.5% each year. The probability of RAMP-DM to have positive incremental effectiveness and negative incremental cost (the southeast quadrant) was 86%.

Supplementary Figure 2 is the CE acceptability curve. The probability of RAMP-DM to be cost-saving (WTP threshold = HK$0) is 0.86. When the WTP threshold increased to HK$20,000 (US$2564), the probability of RAMP-DM to be cost-effective increased to 0.99.

The results of modeling the scenarios which had the effects of RAMP-DM maintained for 5, 8, and 10 years are shown in Table 3. As the effectiveness of RAMP-DM maintain from 5 years to 10 years, the incremental QALY increased from 0.412 to 0.582 per subject in RAMP-DM group. With the assumptions and parameters used in the model, the RAMP-DM group was still cost-saving even if the effectiveness only maintained for 5 years.

The RAMP-DM intervention was found to be cost-saving in all one-way sensitivity analyses (Table 1). The incremental costs for subjects in RAMP-DM varied from −US$1530 to −US$1253 when the programme's on-going costs were varied from the lowest to the highest costs found among the 7 clusters. When the gender-specific HRs of the six complications varied within the 95% CI, the net saving for RAMP-DM in comparison to the usual care group varied from US$1607 to US$1211 per subject and the QALYs gained varied from 0.716 to 0.775. Variations in utility scores associated with individual complications had only very small impacts on the incremental QALYs.

Discussion

This study modeled the long-term cost-effectiveness of on-going RAMP-DM management in addition to usual care in comparison of usual care alone for Chinese DM patients in Hong Kong. RAMP-DM was shown to be cost-saving in terms of gaining 0.807 LYs and 0.745 QALYs at a net saving of US$1404 direct medical cost per subject over a lifetime with the assumptions and parameters used in the model. Applying different assumptions on the cost and effectiveness parameters in the sensitivity analysis, the results all showed RAMP-DM to be cost-saving, indicating the robustness of the findings.

Previous study showed that commonly used existing prediction models were not accurate in our primary care Chinese DM patients [14]. In this cost-effectiveness analysis, we therefore extrapolated the clinical outcomes from empirical data of a 5-year comparative cohort study over the patients' lifetime, instead of using existing prediction models of diabetic complications. The TPs were estimated from the longitudinal observation study findings. The external validity of the model was examined by comparing the modeled life expectancy to that estimated from external sources. A previous study in South Korea found that severe hypoglycaemic events were a strong independent risk factor for CV or all-cause mortality in type 2 diabetic population [39]. In our previous study among 5-year cost-effectiveness of RAMP-DM, the hypoglycaemic events were few (2.6% among RAMP-DM patients, and 3.1% among usual care groups). Therefore, we did not included hypoglycemic events in the model.

It was assumed the effects of RAMP-DM could be maintained over a lifetime in the base case analysis. This was a reasonable assumption since the RAMP-DM intervention is on-going. The costs of RAMP-DM were very low compared to the costs of managing diabetic complications, leading to significant cost-saving from the reduction of complications. With sensitivity analysis under very conservative assumptions that the effects of RAMP-DM sustained only for 5 years and the TPs being the same as those in the usual care group beyond 5 years, the RAMP-DM intervention was still cost-saving.

The incremental effectiveness of RAMP-DM was 1.267 LY and 1.166 QALY (undiscounted) over lifetime. This increments were moderate compared to those found in the Steno-2 study in Denmark, with 1.9 incremental LYs and 1.66 incremental QALYs in the intervention group compared to the usual care group [19]. The Sterno-2 study applied observed CVD event rates within 8 years follow-up to the 1–8 years of lifetime model, and applied the mean event rates for subsequent years assuming that the effects of the multidisciplinary intervention would sustained over a lifetime with age adjustment based on the coefficients of the UKPDS risk predictions models [26, 27]. The age of subjects at entry of the Steno study was 55. Subjects in our study entered the model at 67 years old, which could explain part of the difference in the findings. On the other hand, the CE analysis of the ADDITON-UK trial that extrapolated the 5 years within trial empirical data to a lifetime simulation using the United Kingdom Prospective Diabetes Study Outcomes Model 1 (UKPDS OM1) [21], which showed that the incremental QALY was only 0.047, leading to an ICER of £37,503 that was not cost-effective against the threshold of £30,000. The authors explained that the unfavorable results might due to the introduction of Quality and Outcomes Framework in usual care at the time of trial, which might have reduced the differences in clinical outcomes between the intervention group and usual care. Furthermore, the subjects in this study were recruited at early disease trajectory which might be too early to show the significant effects of the intervention on prevention of CVD events.

The incremental effectiveness value of the CE studies based on short term trials with 1–2 years' follow-up was generally smaller than those found in my study. The stratified patient-centered management programs in the US [23] found incremental effectiveness of 0.54 QALY (undiscounted). A quality improvement collaborative program in the Netherlands gained 0.44 and 0.37 QALY for men and women, respectively [25]. These two studies applied the improvements in HbA1c, blood pressure, and lipid profiles to the UKPDS OM1 [22, 23, 30] and the US CDC (Centers for Disease Control) model [23, 40], respectively, to estimate the lifetime time QALY gained from reduced predicted CVD complications. A protocol-based computerized multifaceted decision support DM management in the UK found only a moderate incremental QALY of 0.037 (discounted at 1.5%) [3]. These studies converted observed changes in HbA1c, blood pressure, and lipid profiles by risk prediction models to TPs of diabetic complications, which might have underestimated the long-term benefits of multidisciplinary management. Besides clinical disease parameters, there are other factors, such as healthy diet [41] and regular physical activity [42, 43], that would also lead to improvements in clinical outcomes.

The significant and sustainable clinical effects of RAMP-DM group might result from several reasons. First, structured risk assessment improved adherence to recommendation on annual assessment to detect and manage reversible risk factors early to prevent further deterioration. Second, significantly higher proportions of subjects in the RAMP-DM group were treated with glucose lowering drugs, insulin, antihypertensive drugs and lipid lowering drugs [15], which suggested that the doctors might have managed the patients more intensively after knowing the risk stratification by RAMP-DM. Third, the risk stratification might also have positive impact on improving patients' consciousness of health and motivating them to change lifestyles. Fourth, the multidisciplinary RAMP-DM team provided more education, e.g., the smoking cessation, about complications prevention, providing patients with additional treatment. Fifth, RAMP-DM also led to significant decreases in HbA1c, blood pressure and LDL-C compared to the control group, which could all lower the complication risks [15].

We observed that RAMP-DM participants had significant reduction in HbA1c, blood pressure, and LDL-C compared to usual care group [15], which could all lower the complication risks. However, RAMP-DM is a multidisciplinary management, the significant clinical effects might also contribute to early detection and management of reversible risk factors, more intensive management from doctors after knowing patients' risk stratification and improvement of patients' consciousness of health and motivation to change lifestyles. All the factors contributed to the clinical effects of RAMP-DM as a whole. Therefore, to simulate the effects of RAMP-DM as a whole, we developed transition probabilities from previous observations and only investigate the effect of non-modifiable factors, i.e., age and sex, on the risk of complications.

There were several strengths in this study. First, the effectiveness in reduction of diabetic complications and the health preference data were from local studies on Chinese DM patients, which should be more valid than adopting data from other populations. Second, the costs of managing DM and diabetic complications were derived from a study on routinely collected data in medical records of primary care Chinese DM patients. Third, the morality estimation took into consideration of the impact of age, sex, and disease status, which had proven external validity.

We should also point out the limitations of the results. First, this study did not simulate the recurrence of the same diabetic complications or the impact of existing complications on the incidences of other complications in the model, which might have led to an underestimation of the incidences of complications and mortality in subjects developed complications in the lifetime simulation. Second, the effectiveness and on-going costs of RAMP-DM intervention was based on the results of a 5-year observational study instead of a RCT. Third, the simulated population was based on our previous study on 5-year cost-effectiveness of RAMP-DM [18]. The previous study was conducted among 8570 RAMP-DM participants and same number of propensity score matched usual care subjects. To evaluate the effectiveness of RAMP-DM on reducing diabetic complications, people with existing complications were excluded. The average age of study population at baseline was 67 years old. The majority of study population were patients with T2DM (99.1%). Therefore, to be accurate, our previous study and this study evaluated the cost-effectiveness of RAMP-DM in comparison with usual primary care among DM patients who had not developed any complication at 67 years old, which were relatively 'healthy' DM patients. The selection bias might affect the generalization of our study findings.

Conclusions

In conclusion, RAMP-DM in addition to usual care could gain an average 0.745 QALY per DM patient from the age of 67 to the end of life. It was cost-saving from the health service provider's perspective over a lifetime in comparison to usual care alone. The program costs per patient were relative low and compensated by the saving of services associated with complications. The evidence supports the provision of RAMP-DM to all DM patients in primary care.

Acknowledgements The authors wish to acknowledge the contributions of the RAMP-DM program teams and Statistics and Workforce Planning Department at the Hong Kong Hospital Authority. Also, we would like to thank all hospital authority cluster coordinators and clinical staff in the Chronic Disease Management Programs for working with our team in this study.

Author contributions F.J. and C.L.K.L. initially conceived the concept of this study. C.S.C.F. and E.Y.F.W. were responsible for data collection. F.J., E.Y.F.W., and A.K.C.C.M. performed the statistical analysis. F.J. drafted the article. All the authors made substantial contribution to the interpretation of data and revised the manuscript for important intellectual content. F.J. and C.S.C.F. take responsibility for the contents of the article.

Funding This study was funded by the Health and Medical Research Fund, Food and Health Bureau, HKSAR Commissioned Research on Enhanced Primary Care Study (Ref. no: EPC-HKU-2). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent While this study involving human participants, all data of the patients were anonymous and extracted by the administrative electronic health record system. Hence, no informed consent of the participants was required in this study.

References

1. International Diabetes Federation: diabetes atlas seventh edition. (2015).
2. American Diabetes Association, Economic costs of diabetes in the US in 2012. Diabetes Care **36**(4), 1033–1046 (2013)
3. F.G. Cleveringa, P.M. Welsing, M. van den Donk, K.J. Gorter, L. W. Niessen, G.E. Rutten, W.K. Redekop, Cost-effectiveness of the diabetes care protocol, a multifaceted computerized decision support diabetes management intervention that reduces cardiovascular risk. Diabetes Care **33**(2), 258–263 (2010). https://doi.org/10.2337/dc09-1232
4. B.S. Chan, M.W. Tsang, V.W. Lee, K.K. Lee, Cost of type 2 diabetes mellitus in Hong Kong Chinese. Int. J. Clin. Pharmacol. Ther. **45**(8), 455–468 (2007)
5. American Diabetes Association, Standards of medical care in diabetes 2013. Diabetes Care **36**(Supplement 1), S11–S57 (2013)
6. National Collaborating Centre for Chronic Conditions: type 2 diabetes National clinical guideline for management in primary and secondary care (update). In. Royal College of physicians, (2008).
7. Canadian Diabetes Association, 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can. J. Diabetes **32**(Supplement 1), S1–S201 (2008)
8. M. Maislos, D. Weisman, Multidisciplinary approach to patients with poorly controlled type 2 diabetes mellitus: a prospective, randomized study. Acta Diabetol. **41**(2), 44–48 (2004). https://doi.org/10.1007/s00592-004-0143-1
9. M.Y. Chen, W.C. Huang, Y.S. Peng, J.S. Guo, C.P. Chen, M.C. Jong, H.C. Lin, Effectiveness of a health promotion programme for farmers and fishermen with type-2 diabetes in Taiwan. J. Adv. Nurs. **67**(9), 2060–2067 (2011). https://doi.org/10.1111/j.1365-2648.2011.05678.x
10. D. Litaker, L. Mion, L. Planavsky, C. Kippes, N. Mehta, J. Frolkis, Physician - nurse practitioner teams in chronic disease management: the impact on costs, clinical effectiveness, and patients' perception of care. J. Interprof. Care **17**(3), 223–237 (2003). https://doi.org/10.1080/1356182031000122852
11. J. Mousques, Y. Bourgueil, P. Le Fur, E. Yilmaz, Effect of a French experiment of team work between general practitioners and nurses on efficacy and cost of type 2 diabetes patients care. Health Policy **98**(2–3), 131–143 (2010). https://doi.org/10.1016/j.healthpol.2010.06.001
12. L.J. Hansen, V. Siersma, H. Beck-Nielsen, N. de Fine Olivarius, Structured personal care of type 2 diabetes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). Diabetologia **56**(6), 1243–1253 (2013). https://doi.org/10.1007/s00125-013-2893-1
13. C.S. Fung, W.Y. Chin, D.S. Dai, R.L. Kwok, E.L. Tsui, Y.F. Wan, W. Wong, C.K. Wong, D.Y. Fong, C.L. Lam, Evaluation of the quality of care of a multi-disciplinary risk factor assessment and management programme (RAMP) for diabetic patients. BMC Fam. Pract. **13**, 116 (2012). https://doi.org/10.1186/1471-2296-13-116
14. F.F. Jiao, C.L. Lam, C. Fung, S.M. McGhee, Comparison of four cardiovascular risk prediction functions among Chinese patients with diabetes mellitus in the primary care setting. J. Diabetes Investig. **5**(5), 606–614 (2014). https://doi.org/10.1111/jdi.12188
15. F. Jiao, C.S. Fung, Y.F. Wan, S.M. McGhee, C.K. Wong, D. Dai, R. Kwok, C.L. Lam, Long-term effects of the multidisciplinary risk assessment and management program for patients with diabetes mellitus (RAMP-DM): a population-based cohort study. Cardiovasc. Diabetol. **14**(1), 105 (2015). https://doi.org/10.1186/s12933-015-0267-3
16. F. Jiao, C.S. Fung, Y.F. Wan, S.M. McGhee, C.K. Wong, D. Dai, R. Kwok, C.L. Lam, Effectiveness of the multidisciplinary Risk Assessment and Management Program for Patients with diabetes mellitus (RAMP-DM) for diabetic microvascular complications: a population-based cohort study. Diabetes Metab. **42**(6), 424–432 (2016). https://doi.org/10.1016/j.diabet.2016.07.030
17. E.Y.F. Wan, C.S.C. Fung, F.F. Jiao, E.Y.T. Yu, W.Y. Chin, D.Y. T. Fong, C.K.H. Wong, A.K.C. Chan, K.H.Y. Chan, R.L.P. Kwok, C.L.K. Lam, Five-year effectiveness of the Multidisciplinary Risk Assessment and Management Programme-diabetes mellitus (RAMP-DM) on diabetes-related complications and health service uses-a population-based and propensity-matched cohort study. Diabetes Care **41**(1), 49–59 (2018). https://doi.org/10.2337/dc17-0426
18. F.F. Jiao, C.S.C. Fung, E.Y.F. Wan, A.K.C. Chan, S.M. McGhee, R.L.P. Kwok, C.L.K. Lam, Five-year cost-effectiveness of the Multidisciplinary Risk Assessment and Management Programme-diabetes mellitus (RAMP-DM). Diabetes Care **41**(2), 250–257 (2018). https://doi.org/10.2337/dc17-1149
19. P. Gaede, W.J. Valentine, A.J. Palmer, D.M. Tucker, M. Lammert, H.H. Parving, O. Pedersen, Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study. Diabetes Care **31**(8), 1510–1515 (2008). https://doi.org/10.2337/dc07-2452
20. S.J. Griffin, K. Borch-Johnsen, M.J. Davies, K. Khunti, G.E. Rutten, A. Sandbaek, S.J. Sharp, R.K. Simmons, M. van den

Donk, N.J. Wareham, T. Lauritzen, Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet **378**(9786), 156–167 (2011). https://doi.org/10.1016/S0140-6736(11)60698-3
21. L. Tao, E.C. Wilson, N.J. Wareham, A. Sandbaek, G.E. Rutten, T. Lauritzen, K. Khunti, M.J. Davies, K. Borch-Johnsen, S.J. Griffin, R.K. Simmons, Cost-effectiveness of intensive multifactorial treatment compared with routine care for individuals with screen-detected Type 2 diabetes: analysis of the ADDITION-UK cluster-randomized controlled trial. Diabet. Med. **32**(7), 907–919 (2015). https://doi.org/10.1111/dme.12711
22. T.P. Gilmer, P.J. O'Connor, J.M. Sperl-Hillen, W.A. Rush, P.E. Johnson, J.H. Amundson, S.A. Asche, H.L. Ekstrom, Cost effectiveness of an EMR-based. Diabetes Clin. Decis. Support Syst. Diabetes **59**, A71–A71 (2010)
23. A.S. Slingerland, W.H. Herman, W.K. Redekop, R.F. Dijkstra, J. W. Jukema, L.W. Niessen, Stratified patient-centered care in type 2 diabetes: a cluster-randomized, controlled clinical trial of effectiveness and cost-effectiveness. Diabetes Care **36**(10), 3054–3061 (2013). https://doi.org/10.2337/dc12-1865
24. R.A. Hirth, M.E. Chernew, E. Miller, A.M. Fendrick, W.G. Weissert, Willingness to pay for a quality-adjusted life year: in search of a standard. Med. Decis. Mak. **20**(3), 332–342 (2000). https://doi.org/10.1177/0272989X0002000310
25. L.M. Schouten, L.W. Niessen, J.W. van de Pas, R.P. Grol, M.E. Hulscher, Cost-effectiveness of a quality improvement collaborative focusing on patients with diabetes. Med. Care **48**(10), 884–891 (2010). https://doi.org/10.1097/MLR.0b013e3181eb318f
26. R.J. Stevens, V. Kothari, A.I. Adler, I.M. Stratton, United Kingdom Prospective Diabetes Study, Group The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin. Sci. **101**(6), 671–679 (2001).
27. V. Kothari, R.J. Stevens, A.I. Adler, I.M. Stratton, S.E. Manley, H.A. Neil, R.R. Holman, UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke **33**(7), 1776–1781 (2002)
28. X. Yang, W.Y. So, A.P. Kong, R.C. Ma, G.T. Ko, C.S. Ho, C.W. Lam, C.S. Cockram, J.C. Chan, P.C. Tong, Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. Am. J. Cardiol. **101**(5), 596–601 (2008). https://doi.org/10.1016/j.amjcard.2007.10.019
29. X. Yang, W.Y. So, A.P. Kong, C.S. Ho, C.W. Lam, R.J. Stevens, R.R. Lyu, D.D. Yin, C.S. Cockram, P.C. Tong, V. Wong, J.C. Chan, Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care **30**(1), 65–70 (2007). https://doi.org/10.2337/dc06-1273
30. P.M. Clarke, A.M. Gray, A. Briggs, A.J. Farmer, P. Fenn, R.J. Stevens, D.R. Matthews, I.M. Stratton, R.R. Holman, Group, U.K. P.D.S. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia **47**(10), 1747–1759 (2004). https://doi.org/10.1007/s00125-004-1527-z
31. F. Jiao, C.K.H. Wong, S.C.W. Tang, C.S.C. Fung, K.C.B. Tan, S. McGhee, R. Gangwani, C.L.K. Lam, Annual direct medical costs associated with diabetes-related complications in the event year and in subsequent years in Hong Kong. Diabet. Med. **34**(9), 1276–1283 (2017). https://doi.org/10.1111/dme.13416
32. F. Jiao, C.K.H. Wong, R. Gangwani, K.C.B. Tan, S.C.W. Tang, C.L.K. Lam, Health-related quality of life and health preference of Chinese patients with diabetes mellitus managed in primary care and secondary care setting: decrements associated with individual complication and number of complications. Health Qual. Life Outcomes **15**(1), 125 (2017). https://doi.org/10.1186/s12955-017-0699-4
33. National Institute for Health and Clinical Excellence: Guide to the methods of technology appraisal 2013. (2013).
34. Census and Statistics Department Gross Domestic Product (GDP), implicit price deflator of GDP and per capita GDP. (2013).
35. World Health Organization: WHO Commission on Macroeconomics and Health: Macroeconomics and health: investing in health for economic development.Report of the commission on Macroeconomics and Health: Executive Summary. World Health Organization, Geneva, (2001).
36. R. Hutubessy, D. Chisholm, T.T. Edejer, Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Eff. Resour. Alloc. **1**(1), 8 (2003). https://doi.org/10.1186/1478-7547-1-8
37. S. Rao Kondapally Seshasai, S. Kaptoge, A. Thompson, E. Di Angelantonio, P. Gao, N. Sarwar, P.H. Whincup, K.J. Mukamal, R.F. Gillum, I. Holme, I. Njolstad, A. Fletcher, P. Nilsson, S. Lewington, R. Collins, V. Gudnason, S.G. Thompson, N. Sattar, E. Selvin, F.B. Hu, J. Danesh; Emerging Risk Factors, C., Diabetes mellitus, fasting glucose, and risk of cause-specific death. N. Engl. J. Med. **364**(9), 829–841 (2011). https://doi.org/10.1056/NEJMoa1008862
38. The World Bank: life expectancy at birth, total (years). Accessed 26 January 2016
39. S.A. Cha, J.S. Yun, T.S. Lim, S. Hwang, E.J. Yim, K.H. Song, K. D. Yoo, Y.M. Park, Y.B. Ahn, S.H. Ko, Severe hypoglycemia and cardiovascular or all-cause mortality in patients with type 2 diabetes. Diabetes Metab. J. **40**(3), 202–210 (2016). https://doi.org/10.4093/dmj.2016.40.3.202
40. R.C. Eastman, J.C. Javitt, W.H. Herman, E.J. Dasbach, A.S. Zbrozek, F. Dong, D. Manninen, S.A. Garfield, C. Copley-Merriman, W. Maier, J.F. Eastman, J. Kotsanos, C.C. Cowie, M. Harris, Model of complications of NIDDM. I. Model construction and assumptions. Diabetes Care **20**(5), 725–734 (1997)
41. K.T. Knoops, L.C. de Groot, D. Kromhout, A.E. Perrin, O. Moreiras-Varela, A. Menotti, W.A. van Staveren, Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA **292**(12), 1433–1439 (2004). https://doi.org/10.1001/jama.292.12.1433
42. P. Kokkinos, Physical activity, health benefits, and mortality risk. ISRN Cardiol. **2012**, 718789 (2012). https://doi.org/10.5402/2012/718789
43. H. Arem, S.C. Moore, A. Patel, P. Hartge, A. Berrington de Gonzalez, K. Visvanathan, P.T. Campbell, M. Freedman, E. Weiderpass, H.O. Adami, M.S. Linet, I.M. Lee, C.E. Matthews, Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA. Intern. Med. **175**(6), 959–967 (2015). https://doi.org/10.1001/jamainternmed.2015.0533