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Research Article

Cost-effectiveness of treatment intervention in prediabetic patients in Bulgaria

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Abstract

Introduction: The study aims to evaluate the cost-effectiveness (CE) of an early intervention in prediabetes (metformin) in order to prevent or slow down the onset of diabetes in those at high risk compared with the current "do nothing" approach.

Materials and methods: An Excel-based model was developed. The results of the CE and cost-utility analyses are presented as an ICER (incremental cost-effectiveness ratio) and ICUR (incremental cost-utility ratio), respectively. Markov model of the cost or potential savings from the perspective of the National Health Insurance Fund in Bulgaria was performed.

Results: The ICER of the metformin intervention in prediabetes patients compared with "do nothing" routine shows that metformin treatment produced more health benefits (number of prevented diabetes cases) on a lower cost for the public payer. The ICER calculated is -7,122.32 BGN per number of prevented diabetes cases and it confirms cost-savings are possible when metformin is applied compared with the "do nothing" approach. The ICUR per quality-adjusted life years (QALYs) gained also shows the metformin preventive intervention as a dominant and cost-saving alternative. The Markov model simulation confirms the intervention with metformin is less costly in a long-term and leads to higher QALYs.

Conclusion: The investment in a preventive intervention with metformin offers an excellent value for money. The ICER of the metformin intervention in prediabetes patients compared with "do nothing" routine shows that metformin preventive intervention produced more health benefits on a lower cost for the public payer in Bulgaria.

Keywords

prediabetes, cost-saving potential, Bulgaria

Introduction

The IDF Diabetes Atlas 10th edition reports a continued global increase in diabetes prevalence, confirming diabetes as a significant global challenge to the health and well-being of individuals, families and societies. Diabetes is shown as a reason for 6.7 million deaths in 2021. It is a cause for at least USD 966 billion dollars in health expenditure – a 316% increase over the last 15 years. 541 million adults have Impaired Glucose Tolerance (IGT, prediabetes), which places them at high risk of type 2 diabetes (IDF Diabetes Atlas 2021).

According to Davies et al. the patients with type 2 diabetes in UK could have a shorter life expectancy. The paper also stated the importance diabetes onset to be prevented through effective measures as lifestyle changes or with use of some medicine-based intervention (Davies et al. 2004). A recent study aims to evaluate and compare the life expectancy in diabetic patients vs. non-diabetic population in Bulgaria. It reports equal life expectancy of both

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groups due to improved control of the disease as well as the associated complications (Tachkov et al. 2020).

Tabak et al. define the state with abnormally high glucose levels but below the diagnostic levels for diabetes as prediabetes or intermediate hyperglycemia. The paper suggest that 5–10% of people per year with prediabetes are expected to progress to diabetes but there is an assumption also the same proportion will convert back to normoglycaemia. Very important is the observation that there is an association between the prediabetes condition and the appearance of early forms of nephropathy, chronic kidney disease, neuropathy, diabetic retinopathy and increased risk of macrovascular disease.. The important positive role of the lifestyle intervention is emphasized (Tabak et al. 2012). Two years earlier Bertram et al. assessed and reported the cost-effectiveness of the screening for prediabetes followed by diet and exercise, or metformin treatment (Bertram et al. 2010).

In 2017, Barry et al. also conclude that lifestyle changes in the high-risk population could prevent the progression to diabetes (Barry et al. 2017).

The delay or the chance the onset of diabetes to be avoided indisputably lead to a lower risk of further complications, keeping or even optimizing the health related quality of life of the patients, prolong their life expectancy and has the potential for reducing the expenditures for medical treatment, social services and reducing the indirect costs due to productivity losses associated long-term with the complications of diabetes.

Progression from prediabetes to diabetes

Around 5–10% of people with prediabetes become diabetic annually although conversion rate varies by population characteristics and the guidelines' definition of prediabetes (Forouhi et al. 2007; Nathan et al. 2007; Tabak et al. 2012). In a meta-analysis of prospective studies published up to 2004, the annualized incidence rates of diabetes for isolated IGT (4–6%) and isolated Impaired fasting glucose (IFG) (6–9%) were lower than those for IFG and IGT combined (15–19%). In the recent major studies, the progression rates have been estimated to be similar: the annualized incidence was 11% in the Diabetes Prevention Program (DPP) Outcomes Study, 6% among participants with IFG in the US Multi-Ethnic Study of Atherosclerosis (MESA), 9% among participants with IFG and 7% among those with an A1c 5.7–6.4% in a Japanese population-based study (Knowler et al. 2009; Heianza et al. 2011; Yeboah et al. 2011). Studies suggest that the risk of diabetes development on the basis of FPG and 2-h postload glucose is broadly similar to that posed by A1c (Gerstein et al. 2007; Zhang et al. 2010). Large randomised control trials, such as the Diabetes Prevention Program (DPP), the Diabetes Prevention Study (DPS), and the Da Qing Study, have systematically proven that the majority of cases of type 2 diabetes can be prevented or delayed (Knowler et al. 2002; Lindstrom et al. 2003; Li et al. 2008). According to the American Diabetes Association (ADA) expert panel, up to 70% of individuals with prediabetes will eventually develop diabetes. In a Chinese diabetes prevention trial, the 20-year cumulative incidence of diabetes was even higher (>90%) among controls with an IGT defined with repeated oral glucose tolerance tests (OGTTs) (Li et al. 2008).

Reversion to normoglycaemia

Several trials have demonstrated reductions in the risk of developing diabetes among prediabetes individuals after lifestyle and medicines-based interventions (Tuomilehto et al. 2001; Knowler et al. 2002; Torgerson et al. 2004; Gerstein et al. 2006, 2007; Ramachandran et al. 2006). Prediabetes may also convert back to normoglycaemia. In a populationbased observational study of the natural history of diabetes in England, 55%–80% of the participants with IFG at baseline had normal fasting glucose at 10-year follow-up (Barry et al. 2017). Other studies have reported lower conversion rates (19% in controls in the DPP Outcomes study) (Knowler et al. 2009).

The health and economic burden of prediabetes

The ADA placed the cost of diagnosed diabetes in 2017 at $327.2 billion (American Diabetes Association 2017). Undiagnosed diabetes (7.9%, $31.7 billion), prediabetes (10.7%, $43.4 billion), and gestational diabetes mellitus (0.4%, $1.6 billion) combine with the prior estimate for diagnosed diabetes to total $403.9 billion annually (Dall et al. 2019). Compared those costs to the U.S. gross domestic product the $403.9 billion economic costs of diabetes and prediabetes are approximately 2.1% of the 2017 U.S. gross domestic product (Bureau of Economic Analysis 2017).

Transition rate from prediabetes to diabetes

Results from a recent study including 10,796 individuals (aged >20 years) with pre-diabetes (according to the IFG-ADA and/or HbA1c-ADA criteria), showed that approximately 70% developed type 2 diabetes within 10 years (DeJesus et al. 2017). A Korean cohort of 406 subjects with pre-diabetes was followed-up every 3–6 months for up to 9 years. They report a transition rate from pre-diabetes to diabetes of 20% (Kim et al. 2014).

Cost-saving potential of preventive interventions

According to Diabetes Prevention Program Research Group, over 10 years, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost-saving compared with placebo. Investment in lifestyle and metformin interventions for diabetes prevention in high-risk adults provides good value for the money spent (Diabetes Prevention Program Research Group 2013).

In Bulgaria currently no preventive initiatives are planned as part of the healthcare for prediabetes patients. It is not recognized as a crucial state where a preventive action can lead to higher quality of life of the population and there is no available assessment of the potential of savings if preventive care is applied.

The aim of the current research is to estimate the cost-effectiveness of the possible interventions in prediabetes patients (treatment intervention) in order to prevent or delay the onset of type 2 diabetes in those at high risk compared with the current "do nothing" approach in Bulgaria. Modeling of the savings was developed using the transition rate from prediabetes to diabetes from the perspective of the society and the payer in Bulgaria.

Methods and materials

An economic evaluation of implementing metformin as a preventative intervention in patients with prediabetes in Bulgaria versus "do nothing" alternative as it is the current situation in Bulgaria was conducted from the perspective of the payer institution National Health Insurance Fund (NHIF). The study was literature-based considering a hypothetical cohort of 1,000 patients due to lack of actual and validated epidemiological data for prediabetes prevalence and incidence and the level of diagnosed patients per year in Bulgaria. The economic evaluation was performed in two consecutive steps: (1) cost-effectiveness analysis using literature data for the number of averted diabetes cases due to treatment with metformin of the identified cases with prediabetes (Knowler et al. 2002); (2) a one-way Markov model using utility data and transition probabilities among different states (normoglycemia, prediabetes, diabetes and death) from the literature (Neumann et al. 2014; Time to Act Now for Prediabetes 2020).

Both analyses were conducted from the perspective of a public payer - the National Health Insurance Fund in Bulgaria as only direct medical costs were considered. The primary economic endpoint was cost per 1 case averted and quality adjusted-life years (QALYs).

The results of the cost-effectiveness analysis and cost-utility analysis are presented by calculation of ICER and incremental cost-utility ration (ICUR) for the outcome and the costs measure, respectively. ICERs represent the additional costs paid per case averted and ICUR - the incremental costs over the QALYs gained. The following formulas were applied:

$$\text{ICER} = \frac{\Delta c}{\Delta E} = \frac{\text{Prediabetes management direct medical costs} - \text{Do nothing direct medical costs}}{\text{Prediabetes management (number of adverted cases)} - \text{Do nothing (adverted cases)}}$$

$$\text{ICUR} = \frac{\Delta c}{\Delta \text{QALY}} = \frac{\text{Prediabetes management direct medical costs} - \text{Do nothing direct medical costs}}{\text{Prediabetes management (QALYs)} - \text{Do nothing (QALYs)}}$$

Measurement of service used and costs

Total monetary costs incurred by a patient included only direct medical costs estimated from the healthcare perspective (NHIF), consisting of the following components: 1) the cost of therapy, 2) routine monitoring laboratory costs; 3) the cost for complications and 4) physician's visits costs. The therapy costs were calculated on a yearly basis using the medicines reimbursed value per pack, referring to the publicly available Positive Drug List, January 2021. The routine monitoring costs, costs for complications and visits were estimated based on the monitoring requirements specified in the pharmacotherapy guidelines and corresponding prices, specified in the National Framework Agreement for 2020–2022 (Clinical paths, CP № 078.1, 192, 088.1) (Tables 1, 2). The probabilities for complications in type 2 diabetes are extracted from published research by Lin et al. 2021 (Lin et al. 2021).

Table 1. Resources used for monitoring and respective costs.

Strategies for diabetes monitoring paid by NHIF	Costs, BGN
Diagnostics and treatment of decompensated type 2 diabetes in adults over 18 ys	702.00
Chemical examination of urine (pH, protein, bilirubin, urobilinogen, glucose, ketons, urine specific gravity, nitrites, white and red blood cells)	1.10
Blood glucose profile	4.50
Glycated hemoglobin	11.00
ASAT	1.50
ALAT	1.50
Alkaline phosphatase (ALP)	1.70
Sodium and kalium	3.40
Lipid profile test (including total cholesterol, LDL, HDL, triglycerides)	5.00
Gamma-glutamyl transferase (GGT) test	1.70
Oral Glucose Tolerance Test (OGTT)	4.70
Prophylaxis examination in adults over 18 ys with high-risk factors for development of diabetes	12.00
Specialized medical examination within dispencary observation for patients with one or more chronic diseases	12.50
Primary specilized examination within dispensary observation	23.00

Effectiveness measurement

The results of the cost-effectiveness analyses are expressed for a 2.8-year time horizon in accordance with the design of Knowler et al. study. The incremental cost-effectiveness ratio (ICER) represents the ratio of the incremental costs over the number of diabetes cases averted. Effectiveness data were based on Knowler et al. study where the incidence of diabetes with the metformin intervention was reduced by 31% (95 percent confidence interval, 17 to 43 percent), as compared with placebo. We used the informal Bulgarian willingness-to-pay (WTP) threshold related to the WHO CHOICE model based on the GDP/capita (GDP/capita for Bulgaria = 17 170 BGN for 2019) (National Statistical Institute 2022).

Table 2. Resources used for complications management and respective costs.

Reimbursed interventions for complications	Cost of 1 CP for 1 pt in 1 year, BGN	Probability of complications onset within 15 years period	Weighted average cost of the complications, BGN
Surgical intervention in diabetic foot without vascular reconstructions	1 230.00	0.01	12.30
Diagnostic and treatment of chronic renal failure in adults over 18 ys	460.00	0.181	83.26

Utility

Utilities values for every stage (normoglycemia, prediabetes, diabetes and death) in the model were obtained from the literature as it was stated above and in Table 3.

Table 3. Utilities values used in the model.

State	Normoglycemia	Prediabetes	Diabetes	Death
Utilities values	0.768	0.738	0.745	0

Structure of the model

We modeled diabetes disease progression in order to estimate cost-effectiveness of treatment interventions in patients with prediabetes in Bulgaria. A Markov model was developed in Microsoft Excel (Fig. 1) for both scenarios - with and without metformin for patients with prediabetes. We assumed a lifelong lifetime horizon as the perspective is the perspective of National Health Insurance Fund. In the Markov model, we used an annual cycle to model the progression of diabetes. In the model, prediabetes patients can be treated with Metformin once prediabetes is detected by screening or diagnosed by symptoms. All probabilities used are presented in Tables 4, 5. The costs and outcomes were presented in discounted and undiscounted values as the discounting rate is 3.5% for both according to the requirements in the HTA guideline for the Bulgarian settings (Ordinance on prices in Bulgaria 2013).

Sensitivity analysis

One-way deterministic sensitivity analyses (Tornado Diagram) were conducted for the costeffectiveness analysis to test the robustness of the results. The costs were varied within a ±5%, ±15% and ±30% intervals, the effectiveness - within a ±5% interval and ICER were recalculated.

Assumptions

The assumptions are related mainly with the transition probabilities obtained from the literature (Time to Act Now for Prediabetes 2020) and precalculated for some of the transitions shown in Tables 4, 5. No information for transition from diabetes to normoglycemia was found and it was assumed as 0.

Table 4. Transition probabilities for the first scenario – intervention with Metformin.

	Normoglycemia	Diabetes**	Prediabetes**	Death*
Normoglycemia	0.5318	0.0072	0.45	0.011
Diabetes**	0	0.895	0.075	0.03
Prediabetes**	0.01713	0.0432	0.93267	0.007
Death*	0	0	0	1

* Tachkov et al. 2019; ** Borissova A-M et al. 2012.

Table 5. Transition probabilities for the second scenario – "do nothing" approach.

	Normoglycemia	Diabetes**	Prediabetes**	Death*
Normoglycemia	0.5318	0.0072	0.45	0.011
Diabetes**	0	0.895	0.075	0.03
Prediabetes**	0.015	0.075	0.903	0.007
Death*	0	0	0	1

* Tachkov et al. 2019; ** Borissova A-M et al. 2012.

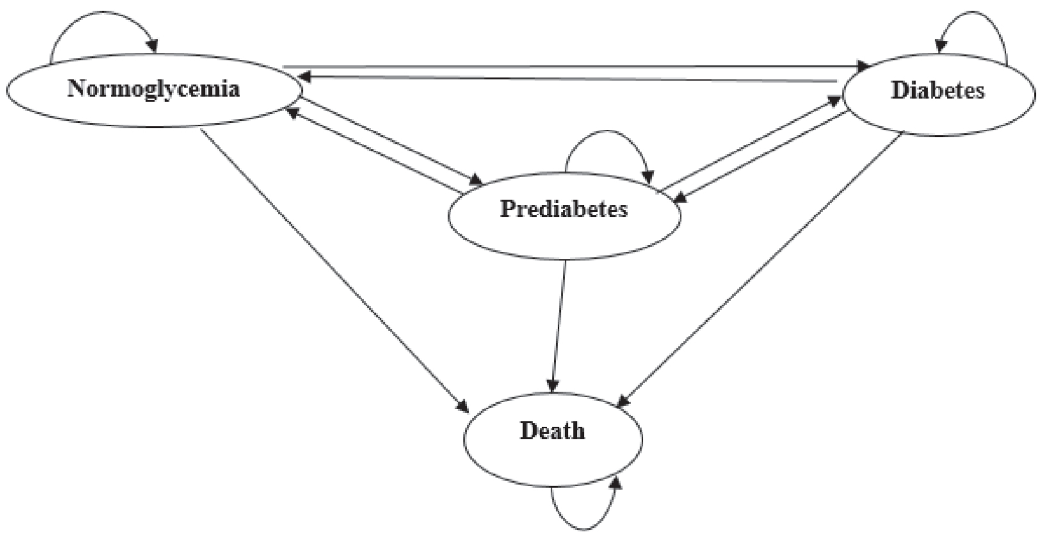

Figure 1. Structure of the model.

Results

Cost-effectiveness analysis

The cost-effectiveness analysis performed compares the current "do nothing" approach with the metformin calculated for a period of 2.8 years based on the approach in the Diabetes Prevention Program Research Group study and the analysis considers the metformin treatment is used for the same period.

The Incremental Cost-effectiveness ratio (ICER) of the metformin intervention in prediabetes patients compared with "do nothing" routine shows that metformin treatment produced more health benefits (number of prevented diabetes cases) on a lower cost for the public payer. The ICER calculated is -7,122.32 BGN per number of prevented diabetes cases and it confirms costsavings are possible when metformin is applied compared with the "do nothing" approach (Table 6).

The Metformin intervention is the less costly and the more effective alternative versus the "do nothing" scenario. It is the dominant alternative and the ICER value is in the 4^{th} quadrant of the Cost-effectiveness acceptability curve (Fig. 2).

The result of the one-way deterministic sensitivity analysis (Tornado Diagram) is shown on Fig. 3. The variation of the costs and the effectiveness impacts the ICERs but constantly confirms the investment in care and treatment of the patients with prediabetes will pays off with future savings and better health outcomes for the protected patients.

Table 6. Cost-effectiveness analysis.

Intervention	Cost*, BGN	Effectiveness **	ΔC, BGN	ΔE	ICER, BGN
Metformin	259,329	310			
Do nothing	2,467,248	0	-2,207,919	310	-7,122.32

* Cost for 1000 adults for 2.8 years; ** number of prevented diabetes cases.

Cost-utility analysis

The Markov model simulation confirms the intervention with metformin is the dominant alternative in long-term vs the current "do nothing" routine - less costly and leads to higher QALY. The cost-utility analysis of the costs and QALYs gained was performed and it shows a cost-saving potential with an ICUR = -1,909.93 BGN per QALY gained. If we apply 3.5% discount rate for both the costs and the QALYs, the ICUR = -2,349.77 BGN (Table 7 and Fig. 4).

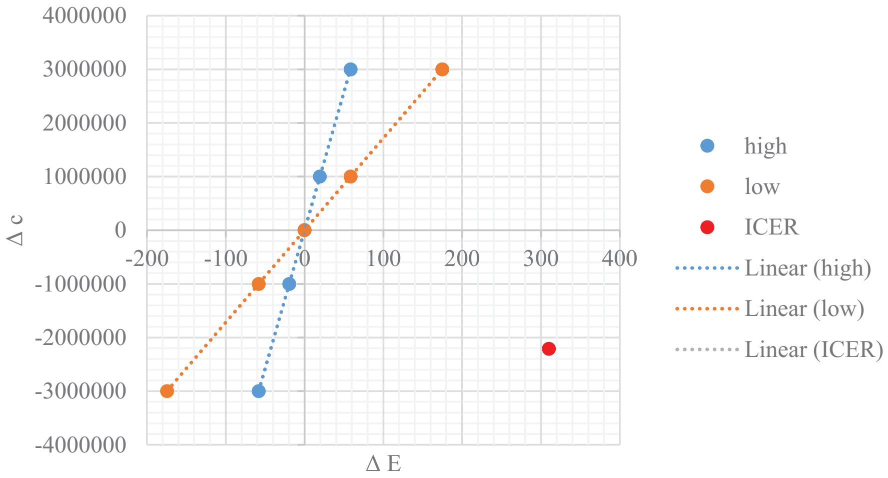

Figure 2. Cost-effectiveness diagram.

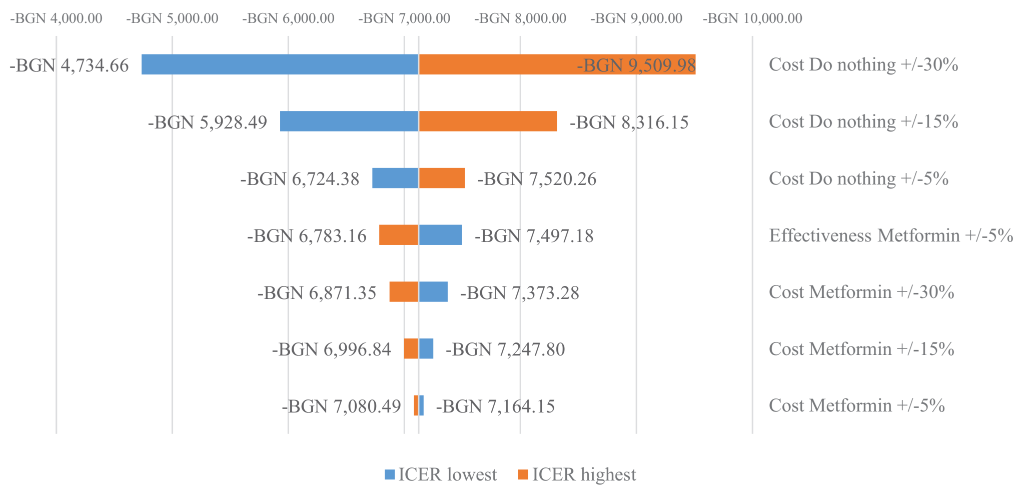

Figure 3. Tornado diagram for costs and effectiveness.

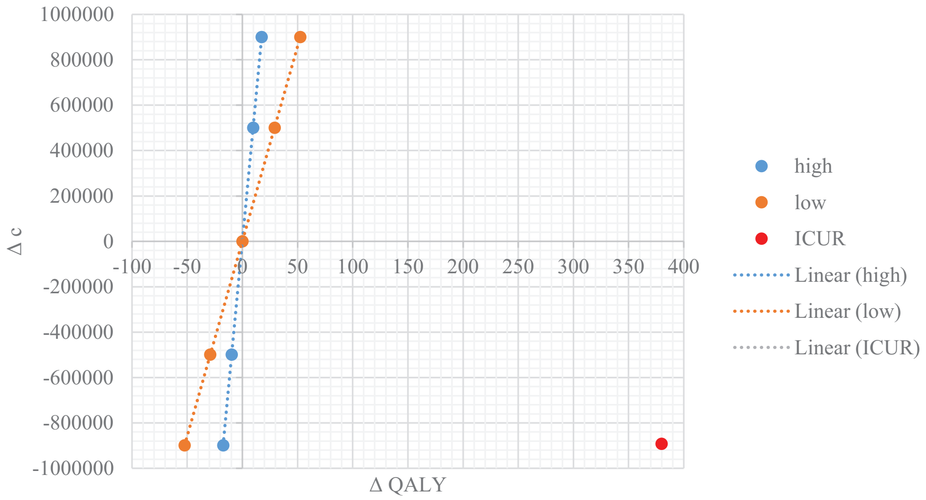

Figure 4. Cost-utility diagram.

Table 7. Cost-utility analysis.

Intervention	SUM Costs	SUM QALY	ΔC, BGN	ΔE	ICUR, BGN
Metformin	3,913,460	13,490			
Do nothing	4,805,672	13,111	-892,213	380	-2,349.77

Discussion

The presented pharmacoeconomic evaluation is the first of its kind from the perspective of the public fund in Bulgaria. It aims to analyze the economic effect of preventive strategies among patients with prediabetes in the country considering a hypothetical cohort of individuals. The study was inspired by the significant economic and social burden of diabetes classified as a socially significant disease. Undoubtedly, diabetes is a disease for which a special medical care is considered in Bulgaria such as education about the disease, interpretation of clinical results, complex assessment of the status of patient with diabetic foot syndrome and neuropathy, anthropometric assessment of the obesity, interpretation of osteodensitometry, glucose levels measurement, consultation with specialist for the high-risk adults, results' assessment within the medical examination of the patients with type 2 diabetes. Moreover, it is recognized as a socially significant disease but there is an unmet need for an early preventive action. However, prediabetes treatment is not publicly financed despite it is a significant risk factor for diabetes development at a later stage. The preventive change in the lifestyle and the treatment with metformin in patients with prediabetes leads to reducing of the onset of type 2 diabetes and its complications. The results from our study, presenting a hypothetical cohort of patients, Highlight the importance and costeffectiveness of these preventive interventions for prediabetes payed with public money. Despite the lack of nationally based data, which could be defined as a strong limitation of the current study, the results are quite similar with the published literature. Moreover, the model could be deemed as a validated one and be used further. They are many studies available, which explore the potential of the preventive interventions to bring savings of the public sources. The DPP Research Group study in 2012 concluded that over 10 years, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost saving compared with placebo. Investment in lifestyle and metformin interventions for diabetes prevention in high-risk adults provides good value for the money spent (Diabetes Prevention Program Research Group 2013). An IDF report from 2016 compared the cost per Quality Of Life Year (QALY) gained from comprehensive lifestyle programs to prevent type 2 diabetes from a health system perspective (International Diabetes Federation 2016).

Despite not being as effective as lifestyle intervention, metformin has been proven to be effective in the primary prevention of type 2 diabetes (Knowler et al. 2002). This combined with the relative low cost of metformin, opens interesting opportunities in terms of cost-effectiveness and cost-savings.

In 2018, Roberts et al. focused their efforts to examine the costs and effects of different intensity lifestyle programs and metformin in participants with different categories of intermediate hyperglycemia. The results show Low-intensity lifestyle programs were the most cost-effective (£44/QALY, £195/QALY and £186/ QALY compared to no intervention in IGT, IFG and HbA1c, respectively). Intensive lifestyle interventions were also cost-effective compared to no intervention (£2775/QALY, £6820/QALY and £7376/QALY, respectively, in IGT, IFG and HbA1c). Metformin was cost-effective relative to no intervention (£5224/QALY, £6842/QALY and £372/QALY in IGT, IFG and HbA1c, respectively), but was only cost-effective relative to other treatments in participants identified with HbA1c. An England-wide program for 50–59 year olds could reduce type 2 diabetes incidence by <3.5% over 50 years and would cost 0.2–5.2% of the current diabetes budget for 2–9 years (Roberts et al. 2018). Based on the UK preventive program results, there is an identified need of a primary preventive program in Bulgaria to be created to promote and support the life-style changes in the high-risk population reported with the highest ICER.

In 2014, a case report based on an information about Diabetic care NPO, Burgas shows the results from a program at a regional level focused on providing care for adult people with multimorbidity. Country experts in 31 European countries identified programs at a national, regional or local level. Programs had to comprise a formalized cooperation between two or more services, of which at least one medical service; and they had to be evaluated - or had an evaluation planned - in some way. The cost savings for local care providers amounted to about 1.2 million BGN (more than 600 000 Euros). Savings are calculated using the price paid to hospitals by the National Health Insurance Fund per amputation, per price of device (e.g. wheelchair) and per payment for a social assistant (ICARE4EU case report 2015).

To the best of our knowledge, no other studies on the cost-effectiveness assessment of a therapeutic intervention in prediabetes patients in Bulgaria are available. The reason probably is the lack of preventive programs and payment of the treatment intervention. The analysis still can be very valuable for the decision makers because it compares the public direct costs and outcomes for the current routine vs the related cost and outcomes of the possible metformin intervention that is affordable and easily can be applied. Considering the perspective, only direct medical costs were included in the model. A broad society-based perspective would distinguish the whole set of benefits brought by the existing preventive strategies for diabetes. Additional research considering local epidemiological and individual level health-utility data as well as broader perspective needs to be performed to find out the possible indirect non-medical costs generated by the morbidity, invalidity and productivity losses associated long-term with the complications of diabetes.

Conclusions

The investment in an intervention with metformin offers an excellent value for money. The ICER of the metformin intervention in prediabetes patients compared with "do nothing" routine shows that metformin intervention produced more health benefits on a lower cost for the public payer in Bulgaria. For a more complete study of the profitability of preventive actions in prediabetes, a methodologically-substantiated program for early diagnosis, timely correction and monitoring of prediabetes in Bulgaria should be developed.

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