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The Effect of Diabetes Prevention on Drug Costs

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Master's thesis

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Costs of diabetes, and Type 2 diabetes particularly, have increased enormously all over the world over the last decades. Drug costs are a remarkable part of the treatment costs of the disease, accounting for around one-fifth of the total healthcare costs for diabetics. In Finland, various reforms of the reimbursement system have been implemented to control drug costs. For instance, in 2017, antidiabetic drugs other than insulins were moved from higher special reimbursement category to the lower special reimbursement category.

The Finnish Diabetes Prevention Study (DPS) was a randomized controlled trial (RCT) that aimed to examine whether Type 2 diabetes can be prevented or delayed by lifestyle modifications. Initially, a total of 522 individuals at high risk of diabetes were randomized to either intervention or control group between 1993–1998. Participants in the intervention group received intensive individual lifestyle guidance, while the control group were offered general advice on reducing diabetes risk at the start of the trial. During the first three years of the intervention, the incidence of diabetes was 58% lower in the intervention group, and the preventative effect was observed to maintain at least for 13 years.

Cost-effectiveness of diabetes prevention is not an unambiguous question. Results from cost-effectiveness analyses based on controlled trials vary, comparing them is challenging, and the results might not be directly applicable when scaling up an intervention into public health care. Simulation of the effects for a wider target group may not be able to take into account all the differences compared with controlled experimental environment, such as participants' selection and participation rate, or differences in target population and in other environment-related factors.

In this thesis, the impact of the DPS-intervention on drug costs was examined over the period of 19 years. Statistically significant results were limited. At the end of the follow-up, cumulative diabetes drug costs were on average €673 ($p<0.01$) lower in the intervention group than in the control group. Cumulative total drug costs were on average, however, €736 ($p>0.05$) higher for the intervention group. This is partly attributed to €356 ($p>0.05$) higher average cumulative costs in cardiovascular drugs for the intervention group. However, the differences concerning total and cardiovascular drug costs were not statistically significant.

In addition to drug costs, the intervention may have affected on several other factors such as health care use or family members of the participants. Moreover, diabetes diagnosis might be experienced as an information shock. This may have affected health behaviour and the measured effectiveness of the intervention. In any case, the overall cost-effectiveness of the DPS cannot be reviewed in this thesis. However, it might be possible to reduce diabetes drug costs through lifestyle intervention. Hence, it would be reasonable to examine if the equivalent savings in diabetes drug costs, or cost-effective health improvements, could be reached by the intervention implemented in public health care, compared to repeated cuts in drug reimbursement system. These reimbursement cuts might eventually increase the use of expensive health care services due to poorer drug adherence. A successful intervention might appear as a reduced use of health care services or improved labour market outcomes. However, additional research is needed especially regarding the cost-effectiveness of the diabetes prevention interventions in public health care.

Key words: Diabetes prevention, drug costs, cost-effectiveness

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Diabeteksen, ja erityisesti tyypin 2 diabeteksen, kustannukset ovat kasvaneet koko maailmassa räjähdysmäisesti viime vuosikymmeninä. Lääkekustannukset ovat merkittävä osa diabeteksen hoidon kustannuksia kattaen Suomessa noin viidenneksen diabeetikoiden terveydenhuollon kokonaiskustannuksista. Suomessa lääkekustannuksia on pyritty hillitsemään muun muassa erilaisilla lääkekorvausjärjestelmän reformeilla. Esimerkiksi vuonna 2017 diabeteslääkkeet siirrettiin insuliineja lukuun ottamatta ylemmästä erityiskorvausluokasta alempaan.

Suomalainen tyypin 2 diabeteksen ehkäisytutkimus (DPS) oli randomisoitu kontrolloitu koe (RCT), joka pyrki selvittämään, voidaanko diabetesta ehkäistä elintapaohjauksella. Alun perin 522 korkeassa diabetesriskissä olevaa henkilöä jaettiin satunnaisesti interventio- ja kontrolliryhmiin vuosina 1993–1998. Interventioryhmän jäsenille tarjottiin yksilöllistä tehostettua elintapaohjausta ja vertailuryhmälle yleisiä neuvoja diabetesriskin pienentämiseksi intervention alussa. Ensimmäisen kolmen vuoden aikana diabeteksen esiintyvyys oli 58 % pienempi interventioryhmässä ja ehkäisevän vaikutuksen havaittiin säilyvän ainakin 13 vuotta.

Diabeteksen ehkäisyn kustannusvaikuttavuus ei ole yksiselitteinen kysymys. Kontrolloituihin kokeisiin perustuvien kustannusvaikuttavuusanalyysien tulokset vaihtelevat, niiden vertaaminen on haastavaa, eivätkä saadut tulokset välttämättä ole suoraan hyödynnettävissä interventiota skaalattaessa julkiseen terveydenhuoltoon. Vaikutusten simulointi laajemmalle kohdejoukolle ei välttämättä pysty huomioimaan kaikkia eroja kontrolloituun koeympäristöön verrattuna, kuten henkilöiden osallistumisastetta ja valintaa, tai eroja kohdejoukossa ja muissa ympäristöön liittyvissä tekijöissä.

Tässä tutkielmassa tarkasteltiin DPS-intervention vaikutuksia lääkekustannuksiin 19 vuoden aikaperiodilla. Tilastollisesti merkitsevät tulokset olivat vähäisiä. Diabeteslääkkeiden kumulatiivisten kustannusten havaittiin olleen seurantajakson lopussa keskimäärin 673 ($p<0.01$) euroa pienemmät interventioryhmässä. Kumulatiiviset kokonaislääkekustannukset olivat kuitenkin interventioryhmässä keskimäärin 736 ($p>0.05$) euroa suuremmat verrattuna kontrolliryhmään. Tämä selittyy osittain interventioryhmän 356 ($p>0.05$) euroa korkeammilla keskimääräisillä sydän- ja verisuonisairauksien kumulatiivisilla lääkekustannuksilla. Vaikutukset kokonaislääkekustannuksiin ja sydän- ja verisuonitautilääkkeiden kustannuksiin eivät kuitenkaan olleet tilastollisesti merkitseviä.

Lääkekustannusten lisäksi interventio on saattanut vaikuttaa useisiin muihin tekijöihin, kuten osallistujien terveydenhuollon käyttöön tai perheenjäseniin. Diabetesdiagnoosi saatetaan lisäksi kokea informaatioshokkina, mikä on saattanut vaikuttaa osallistujien terveyskäyttäytymiseen ja intervention mitattuun tehokkuuteen. DPS-intervention kustannustehokkuutta ei joka tapauksessa voida arvioida tässä tutkielmassa. Diabeteslääkekustannuksia saattaa kuitenkin olla mahdollista hillitä elintapainterventiolla. Siksi olisi hyödyllistä tutkia, olisiko terveydenhuollossa toteutettavalla interventiolla mahdollista päästä yhtä suuriin diabeteslääkekustannusten säästöihin, tai kustannusvaikuttaviin terveyden paranemiin, kuin toistuvilla lääkekorvausten leikkauksilla. Leikkaukset saattavat lopulta lisätä kalliiden terveydenhuoltopalvelujen käyttöä huonomman lääketunnollisuuden myötä. Onnistunut interventio voisi näyttäytyä esimerkiksi vähäisempänä terveydenhuoltopalvelujen käyttönä tai parantuneina työmarkkinatulemina. Kustannusvaikuttavan intervention toteuttamisesta terveydenhuollossa tarvitaan kuitenkin vielä lisää tutkimustietoa.

Avainsanat: Diabeteksen ehkäisy, lääkekustannukset, kustannusvaikuttavuus

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1 Introduction

The past decades have established the role of Type 2 diabetes as one of the most significant challenges of human health and health care systems (Zimmet et al. 2001; Chen et al. 2012; Lin et al. 2020). A remarkable increase in the prevalence of the disease has been observed, as the human environment and lifestyles have changed along the economic development and urbanization (Whiting et al. 2011, 311). In 2021, approximately 537 million adults worldwide were suffering from diabetes and the number is estimated to reach 643 million by 2030. (International Diabetes Federation 2021). According to World Health Organization (2022), over 95 percent of diabetes patients have Type 2 diabetes. The association with several serious complications, such as heart attacks and strokes, makes Type 2 diabetes one of the most expensive diseases (Rosella et al. 2016, 395). Therefore, the direct and indirect health and economic impacts of the disease are nowadays extensively examined.

The increasing prevalence of Type 2 diabetes is associated with higher consumption of diabetes medication and hence with larger private and public expenditures. According to Jarvala et al. (2010; 17, 27), drug costs account for around 25 % of the total healthcare costs for diabetics. In Finland, a significant portion of diabetes drugs and diabetes related drugs are either fully or partially reimbursed by the Social Insurance Institution of Finland. In 2019, 394 000 Finnish individuals received reimbursements for diabetes drugs, which represented 7.1 % of the total population of Finland. Additionally, 182 million euros were allocated for reimbursing diabetes medication in the same year, accounting for almost 12 % of the total amount reimbursed for drugs. (Kelasto 2023.)

As the incidence of Type 2 diabetes has been constantly increasing over the past decades, prevention of the disease has become even more crucial. Therefore, several studies have pointed out the potential of lifestyle interventions implemented for subjects at high risk of Type 2 diabetes (Zimmet et al. 2001, 783). The Finnish Diabetes Prevention Study (DPS) was a randomized controlled trial (RCT) that aimed to examine whether Type 2 diabetes could be prevented or delayed by lifestyle changes. Initially, a total of 522 middle-aged and overweight individuals with impaired glucose tolerance (IGT) were randomized to either intervention or control group between years 1993–1998. The intervention included for instance individualized dietary counselling and advice for improved physical activity. The control group was offered general advice on reducing

diabetes risk at the start of the trial. (Uusitupa et al. 2000, 137–140.) During the first three years, the incidence of diabetes was found to be 58 % lower in the intervention group, compared with the control group. The risk reduction was observed to persist for at least 13 years. Moreover, weight reduction was greater, and values of clinical and metabolic parameters were improved more in the intervention group than in the control group. (Lindström et al. 2003; Lindström et al. 2013.)

In this thesis, I study the impact of the lifestyle intervention on drug costs using data from the DPS. I classify the drug groups by ATC-codes controlled by WHO. In addition to diabetes drugs, I analyse the impact on cardiovascular drugs costs. For instance, Gong et al (2019) found that lifestyle intervention reduced cardiovascular disease events and deaths in Chinese Da Qing study. Follow-up period of 19 years is observed in this thesis. This is exceptionally long compared with usual RCT-based studies. Moreover, this thesis is the first to present the effects of the intervention in DPS on drug costs.

I start by introducing the DPS, its objectives, methods, and results in Chapter 2, since the trial is closely related to my thesis. In Chapter 3, I shortly introduce the Finnish drug reimbursement system and its most remarkable reforms during the years considered in this thesis. In this context, I also review the development of diabetes drug costs in Finland based on statistical data. In Chapter 4, I discuss the diabetes prevention as a tool of cost-savings, the challenges of scaling up interventions to a broader target group, as well as how wider implementations may differ in terms of costs and effectiveness compared with clinical trials. In Chapter 5, I introduce the data and methods used in this thesis and examine the impact of the lifestyle intervention on drug costs. Finally, in Chapter 6, I discuss the results of this thesis.

2 The Finnish Diabetes Prevention Study

2.1 Background

In this chapter, I introduce the Finnish Diabetes Prevention Study (DPS). I am not part of the original study group, but I utilize the study design, data, and results of the DPS as studying the impact of the intervention on drug costs. Presentation of the screening process, intervention, and results of the DPS is based on previous papers by the researchers involved (e.g., Eriksson et al. 1999; Uusitupa et al. 2000; Lindström et al. 2003; Lindström et al. 2008; Lindström et al. 2021).

The strong relationship between Type 2 diabetes and lifestyle factors has long been recognized (e.g., Pan et al. 1997; Haffner 1998; Uusitupa et al. 2000). DPS was started in 1993 aiming to investigate if the Type 2 diabetes can be prevented or delayed by lifestyle modifications. Between the years 1993 and 1998 a total of 522 subjects with impaired glucose tolerance (IGT) where randomly assigned to either intervention group or control group. The intervention included frequent dietary advice and guidance to increase physical activity. The main idea was to compare if the cumulative incidence of Type 2 diabetes differs between the intervention and the control group during the years followed up. The study was implemented as a multicentre study in Helsinki, Kuopio, Turku, Tampere, and Oulu. (Uusitupa et al. 2000, 138–139; Eriksson et al. 1999, 794.)

2.2 Screening

The subjects at high risk of developing Type 2 diabetes were prioritized in the screening program of DPS. Potential participants were selected, for instance, from epidemiological surveys and by opportunistic population screenings[1]. The inclusion criteria targeted middle-aged (44–64) overweight subjects with Body Mass Index (BMI) > 25 kg/m^2 and IGT based on the WHO criteria. According to the criteria, individuals with two hours tested plasma glucose between 7,8 mmol/l and 11,1 mmol/l and fasting plasma glucose less than 7,8 mmol/l have IGT. (Lindström at al. 2003, 3230; Uusitupa et al. 2000, 138.)

[1] Epidemiological survey can include for instance online or face-to-face surveys, as well as phone interviews (Safdar et all. 2016). Opportunistic screening indicates a check or test offered by a health professional, which can be used to early detection of a disease (Uittenbogaart et al. 2020).

Participants were included through two separate screenings. The first oral glucose tolerance test (OGTT) was followed by the second two hours OGTT for those with IGT based on the first test. The IGT criterion that needed to be met was measured from the mean value of the second test. Around 90 percent of the subjects were enrolled by this approach. However, since the two-state criterion was designed after the start of the screening, the first 10 percent were included based only on the first OGTT, or on the combination of high plasma glucose and high two hours plasma glucose levels. (Eriksson et al. 1999, 795.)

A subject was excluded from the study if she or he had previous diagnosis of diabetes, except gestational diabetes. In addition, vigorous exercise, medical glucose lowering treatment, chronic disease or any other medical condition which could, with high probability, lead to death during the following six-year period or affect the glucose metabolism, were all used as exclusion criteria. (Uusitupa et al. 2000, 138.)

2.3 The Intervention

DPS subjects were randomly divided into two separate groups; the intervention group which received intensive and frequent lifestyle modification advice, and the control group receiving significantly less guidance on reducing the risk of Type 2 diabetes. At the beginning of the trial, however, the control group was given general information about healthy lifestyle. For instance, they were guided to reduce BMI below 25 kg/m^2 and to gain most of the daily energy (70%) from nutrients other than fat. In addition, they were recommended to stop smoking and to reduce the use of alcohol. (Eriksson et al. 1999, 795.)

The lifestyle intervention programme provided for the intervention group included individually designed exercise program and frequent dietary advice offered both individually and within group sessions (Uusitupa et al. 2000, 139)[2]. During the first year of the intervention the subjects had seven face-to-face consultation visits with the nutritionist and every three months from then on. In addition, voluntary group sessions were also offered as well as lectures, cooking lessons, grocery store visits and remote communication. Even though the primary goals were set at the group level before the start

[2] The idea of adding physical exercises into the intervention programme was based on the feasibility study of Eriksson & Lindgärde (1991). The suitable diet was in turn learned from the dietary pilot study implemented for a subgroup of DPS subjects (Sarkkinen et al. 1996). (Lindström et al. 2003, 3231.)

of the intervention, sessions were organized to focus on individual targets. The aim was to provide necessary information and skills to achieve permanent lifestyle changes step by step. (Lindström et al. 2003, 3231.)

For most subjects in the intervention group the primary goal was to lose 5–10 kg, or 5 percent of body weight. Individual dietary plan, which was based on three-day food records measured from each subject, was designed by a professional nutritionist. The aim of the plan was to encourage subjects to consume the recommended allocation of nutrients: at least 50 % of daily calories from carbohydrates, under 10 % from saturated fat, and 20 % from mono- and polyunsaturated fat (or 25 % at the most if the five percent surplus included monounsaturated fat only). With these modifications a daily cholesterol intake was planned to stay under 300 mg. In addition, the importance of fibre intake was emphasized. The recommended amount of fibre was at least 15 g per 1000 kcal. (Uusitupa et al. 2000, 139; Eriksson et al. 1999, 795.)

Increased physical activity was one of the main goals for every subject in the intervention group. Individual guidance was given by the nutritionists and physicians, and group training, walking, and hiking sessions were provided during the intervention. Subjects were also encouraged for better results by competitions organized between the participating centres. (Lindström et al. 2003, 3231.)

2.4 Results

The intervention improved physical activity of the intervention group. At year 1, the share of sedentary individuals was 14 % in the intervention group and 30 % in the control group, respectively. Corresponding proportions were 17 and 29 % at year 3. Dietary intake improved more in the intervention group: fat and energy intake were reduced and the percentage of carbohydrates of daily energy were increased, compared with the control group. In the intervention group, 37, 21 and 37 % of the subjects reached the fat intake, saturated fat intake and the fibre density goal. The corresponding proportions were 20, 9 and 23 % in the control group. (Lindström et al. 2003, 3233.)

Improved physical activity and dietary changes resulted in desired goals more often in the intervention group. In the intervention group, 46 % lost more than 5 % of weight during the first year. The corresponding proportion in the control group was 14 %. The average weight loss in year 1 was 4,5 kg for the intervention group and 1,0 kg for the

control group. After three years of the intervention the corresponding numbers were 3,5 and 0,9. (Lindström et al. 2003, 3233.) Weight reduction of 1 % was estimated to reduce the risk of diabetes by 7 % (Lindström et al. 2021). Compared with the control group, more improvement was also observed for the intervention group in the values of clinical and metabolic parameters such as fasting plasma glucose, 2-h plasma glucose, HbA_{1c} and high-density lipoprotein (Lindström et al. 2003, 3233).

Diabetes was diagnosed for 9% of the intervention group and for 20% of the control group during the first three years of the intervention, meaning 58% lower incidence in the intervention group (Lindström 2003, 3234). The effect was independent of the baseline weight, glucose, gender, socioeconomic status, or educational attainment but was however slightly higher among patients over 60 years old (Lindström et al. 2008; Wikström et al. 2009). The intervention lasted on average for four years but in the follow-up the preventive effect of the intervention was observed to maintain at least for 13 years. During the total follow-up period of 16 years, 106 diabetes cases were diagnosed in the intervention group and 140 in the control group, respectively. (Lindström et al. 2013.)

When aiming to prevent Type 2 diabetes, the objective is also to affect diabetes related diseases, which cause most of the costs, disability and mortality among diabetics (Lindström et al. 2021). After nearly 14 years of follow up the difference in mortality and cardiovascular morbidity between the intervention and the control group was not observed (Uusitupa et al. 2009). Evidence of long-term impacts of diabetes prevention on the incidence of additional diabetes related diseases remained limited (Lindström et al. 2021).

3 Diabetes drug costs in Finland

3.1 The Finnish reimbursement system

3.1.1 The system today

The purpose of Chapter 3 is to describe diabetes drug costs in Finland, where they come from and how they have developed over the years. Therefore, it is appropriate to introduce the Finnish pharmaceutical reimbursement system first. The aim is to provide a short description of the system under which the target population of this thesis have been, and how they may have been affected by the modifications of it.

In Finland, reimbursement for the costs of prescription drugs is covered for all insured residents by the Health insurance act (1224/2004). The purpose is to guarantee the access for an insured resident to necessary drugs for reasonable outpatient care costs (Government proposal 330/2014). The medical product, brand name drug or comparable generic product defined by Finnish Medicines Agency (Fimea), is reimbursed directly at the pharmacy if it fulfills the requirements of a prescription drug under Medicines act (395/1987) and is prescribed to cure the disease or to relieve its symptoms. In addition, a valid approval of Pharmaceutical Pricing Board (Hila), which also defines the reasonable wholesale price for a drug, is required for a drug to be reimbursed. (Health insurance act 1224/2004, 5:1.) The reimbursement is paid by the Social Insurance Institution of Finland (Kela), which is also responsible for implementation of the Act as well as monitoring the compliance of it. (Vuorenkoski et al. 2003, 170; Health insurance act 1224/2004). The funding of the medical care insurance comes from state, employers, entrepreneur, and beneficiaries (Social Insurance Institution of Finland 2023d).

Since year 1986, as the lower special rate of reimbursement was introduced, the Finnish reimbursement system has been divided into three levels: basic rate of reimbursement, lower special rate of reimbursement and higher special rate of reimbursement (Health insurance act 479/85, 5 §). The rates have been adjusted repeatedly during the last decades. According to the Social Insurance Institution of Finland (2023c), the rates are 40, 65 and 100 percent at the moment. The initial deductible (€50) of reimbursable drugs is paid annually by the customer before reimbursements are available. When the annual maximum (€592.16 in 2023) of drug expenses is met, the customer pays €2.50 for each purchase. (Social Insurance Institution of Finland 2023c.)

The severity of the disease and the drug dependency of its treatment are the main factors determining the rate of reimbursement (Medaffcon 2020). For instance, A10A-classified insulins are (Social Incurance Institution of Finland 2023a), and according to the DPS data, have been over the whole period considered in this thesis, reimbursed with the higher special rate of reimbursement. This is, after the initial deductible of €50 is met, insulin purchases are fully reimbursed, but however, up to the annual maximum. From that on the patient pays €2.50 for each purchase. The antidiabetic drugs classified under the ATC-code A10B are nowadays reimbursed with the lower special rate (Social Insurance Institution of Finland 2023a). Cardiovascular drugs are as well, in case of being serious and chronic, reimbursed with the lower special rate, as it has been stated by the government (Government proposal 184/2016) that the lifestyle modifications are crucial factors in preventing and treating these diseases.

3.1.2 The most remarkable reforms

The system has been modified several times during the period considered in this thesis. Controlling continuously growing drug costs has usually been the main goal with these modifications (see e.g., Government proposal 250/1993; 97/2005). For instance, when the lower special rate of reimbursement was introduced in 1986, the reimbursement rate was set to 90 percent. The basic rate was set at 50 percent of the cost exceeding 20 marks. (Health insurance act 479/85, 5 §.) However, at the end of the 1993, the first year of the intervention, the lower special rate was cut to 75 percent of the cost exceeding 25 marks. In addition, corresponding initial deductible of 25 marks was introduced also for the higher special rate. At the same time the initial deductible for the basic rate was raised to 50 marks. (Health insurance act 1644/1993, 9 §.) The reform affected the treatment cost for diabetics as all the diabetes drugs were at that time reimbursed with higher special rate. The initial deductible of 25 marks had to be paid for each purchase.

Generic substitution was introduced in 2003. Likewise in most of the former modifications, the aim was to contain drug costs. Pharmacists were obligated to offer the cheapest or nearly cheapest substitute for a drug prescribed by a physician or dentist. However, the substitution was made only with the permission of the customer and the physician. Moreover, the customer's choice between the prescribed product and the cheaper generic product did not affect to the reimbursement he or she was paid. (Medicines act 80/2003.) For instance, antidiabetic drugs (A10B) were fully reimbursed

despite the customer's choice to reject the substitution. However, for instance metformin[3], the priority antidiabetic drug for Type 2 diabetics, has been substitutable at least since 2004 (Fimea 2023). Therefore, the reform might have affected the reimbursement expenses of diabetes drugs. On the other hand, insulins are not included in generic substitution (Aaltonen et al. 2018; HE 314/2022), so the reform likely did not affect the reimbursement expenses of them.

The reference price system introduced in 2009 extended the generic substitution. It was assumed to improve sustainability of the system by ensuring the use of the most cost-effective medical treatment (Government proposal 100/2008). According to the Health insurance act (802/2008) a reference price group consists of reimbursable and substitutable drugs with the equal amount of the same pharmaceutical ingredient. In addition, the products within the same group must have the same dosage form and approximately identical package size. Within the reference group, VAT-inclusive retail price of the cheapest medical product (nowadays added with €0.5) determines the reference price of the group. A drug purchase is reimbursed based on the reference price of the group the drug is included into. (Health insurance act 802/2008.) If the generic substitution is refused by the patient, he or she pays the price exceeding the reference price added with copayment (Social Insurance Institution of Finland 2023b). This is, to be reimbursed according to the health insurance, the consumer has to choose the cheapest possible drug (Aaltonen et al. 2018).

In addition, smaller reforms have been implemented during the follow-up period of this thesis. In 2005 the initial deductible paid for each drug purchase was removed. Instead, the initial deductible, similar to the one currently in place, assessed on calendar year basis was introduced. Moreover, reimbursement rates were adjusted to new levels of 40, 72 and 100 percent. (Health insurance act 885/2005.) In 2012 the lower special rate was lowered to its current level of 65 percent. The basic rate was cut to level of 35 percent in the same year but was, however, raised to its current level of 40 percent in 2015. (Health insurance act 622/2012; 252/2015.)

In 2017, the reimbursement rate of antidiabetic drugs (A10B) was lowered from 100 to 65 percent. The reform was a part of the acts implemented by Finnish government, that

[3] Biguanides, which include metformin, has been used to treat diabetes more than 50 years. Metformin reduces hepatic glucose production which decreases blood glucose levels. (Eriksson & Laine 2013.)

aimed to save €150 million of drug reimbursement expenditures. (Government proposal 184/2016) Compared with 2016, the use of antidiabetic drugs decreased by 1 % in 2017. At the same time, the number of patients entitled to receive reimbursement for these drugs increased by 3 %. (Suviranta et al. 2019.) Even though the causal link between the reform and drug consumption cannot be interpreted through these statistics, it has been shown also in previous studies that copayment correlates negatively with adherence to diabetes drugs (Barron et al. 2008; Chernew et al. 2008; Colombi et al. 2008). Since better adherence to drugs has been found to lower health care costs by reducing for instance emergency department use (Stuart et al. 2009; Roebuck et al. 2011) and reduce indirect costs such as absences due to illness (Rizzo et al. 1996), the effectiveness of the reform could be questioned. In addition, the reform has been criticized on equity issues, as it affects the most the low-income patients and elderly (Diabetesliitto 2021; Government proposal 184/2016).

3.2 Statistics

The modifications of the reimbursement system are not assumed to affect the interpretation of the effects examined in this thesis since the DPS groups have been randomly assigned[4]. In addition, when modelling the impacts of the intervention, it is possible to control time variant factors, as suggested later in Chapter 5. However, the amendments during the past decades clearly reflect the pressure of containing the growing drug expenditures (see e.g., Government proposal 250/1993; 97/2005). More controlled, structured, and multifaceted system has been the result of this trend (Medaffcon 2023).

Remarkable increase in the numbers of diabetes patients has been seen all over the world, both in high-income countries and low- and middle-income countries (Seuring et al. 2015, 812). Finland is not an exception in this regard. Figure 1 illustrates the amount of Finnish people entitled to the special rate of reimbursement due to diabetes, as a share of total Finnish population. In Figure 1, the special rate indicates both higher and lower special rate of reimbursement. Hence, the share consists of the sum of patients entitled to either one or both rates due to diabetes. In addition, in Figure 1 the share contains both, entitlements for special rate of reimbursement due to type 1 and type 2 diabetes. However, in Finland 75–80 percent of diabetes patients have type 2 diabetes (Ilanne-Parikka, 2021).

[4] This is, selection bias is assumed to be zero (see e.g., Angrist & Pischke 2008, 12–16).

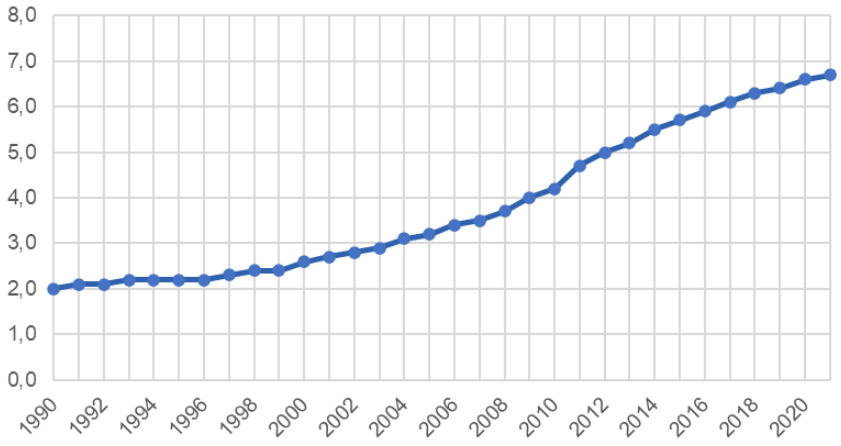

Figure 1: Patients entitled to the special rate of reimbursement due to diabetes, % of Finnish population (Sotkanet 2023a)

According to Figure 1 the share has increased nearly five percentage points over the last three decades. The number of persons has grown from 100023 to 373474 people in 31 years. The growth of the share has been fastest in the 2000s being on average 5.3 % per year. The corresponding numbers of the 1990s and the 2010s are 2.1 and 4.8 % per year. As summarized in Chapter 2, lifestyle factors are strongly associated with Type 2 diabetes (Pan et al. 1997; Haffner 1998). For instance, according to Sotkanet (2023b) the share of obese individuals in Finland has increased by five percentage points over the last nine years. This might partly explain the increase in diabetes reimbursement entitlements. However, changes in lifestyles are not the only explanation for the increased numbers of diabetes. For instance, it is commonly known that Finnish population is aging. Type 2 diabetes is more likely in the elderly (Reini & Honkatukia 2016; Linström et al. 2013). Therefore, a growing portion of the Finnish population is at risk of diabetes.

Figure 2 illustrates the development of costs and the number of insulin and antidiabetic drug users in Finland since the year 1993. Inflation adjustment to 2021 currency has been made using the cost-of-living index (Consumer price index 2022). According to Figure 2, costs and the number of users for both groups increased steadily over the 1990s. The costs of insulin were at their highest in 2011 being over €114 million. The most interesting point is at the turn of the 2010s where the costs of antidiabetic drugs (A10B) start to rise more sharply compared with previous decades, whereas the cost of insulins (A10A) begins to fall around the same years. The costs of antidiabetic drugs are at their highest in 2021 being over €170 million. The continuous increase in the numbers of drug users is also noteworthy, especially in insulins, as it shows that not all the variation in cost

developments can be explained by the increase in diabetes patients. The number of insulin and antidiabetic drug users were around 130 000 and 356 000 in 2021.

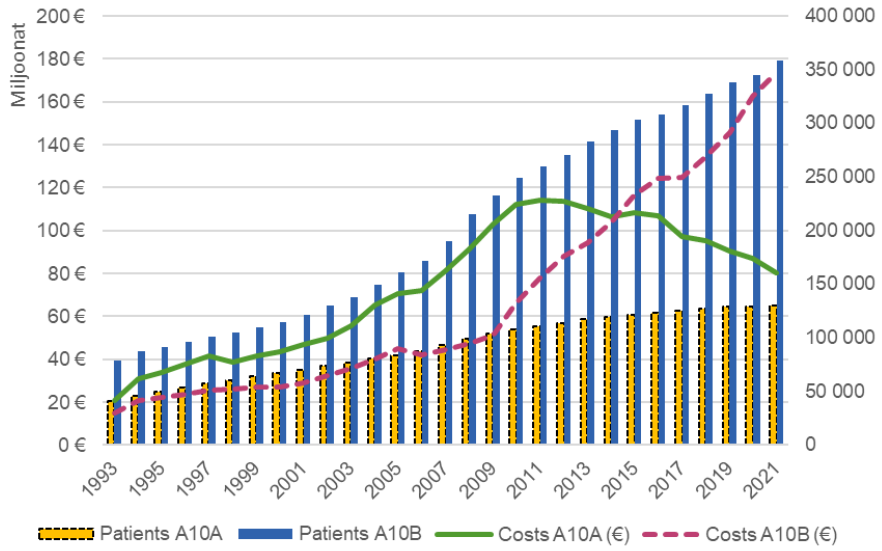

Figure 2: Users and costs of insulin (A10A) and antidiabetic drugs (A10B) in Finland (Kelasto 2023)

Although the economic burden of diabetes has grown, the increased incidence of the disease is not the only explanation for this trend. Treatment of diabetes has evolved as new, however more expensive, drugs have reached the market (Soppi et al. 2018). While metformin has remained as the priority drug for Type 2 diabetics, alternative treatments such as inhibitors of sodium-glucose cotransporter 2 (SGLT2), glucagon like peptide 1 (Glp-1) analogues and gliptins (DPP-4 inhibitors) have been introduced in recent years. These recently developed drugs have been shown to have cardiac and renal effects that improve the prognosis of Type 2 diabetes. (Niskanen & Laine 2020.)

As it has been commonly identified, diabetes related complications cause the majority of diabetes costs (see e.g., Henriksson et al. 2000; Jarvala et al. 2010; Li et al. 2013). The new drugs are more expensive compared with traditional treatment, and therefore might appear as increased diabetes drug costs in Figure 2. However, their net effects on total diabetes costs might be negative if the risk of expensive complications can be reduced. This risk reduction, for instance in coronary heart disease, might appear not only as reduced health care costs (Stuart et al. 2009; Roebuck et al. 2011), but also as improved labour market outcomes (Rizzo et al. 1996; Stephens & Toohey 2022), as the disease and its complications do not harm income generation or work efficiency.

For instance, Empagliflozin, SGLT2-classified drug, which have had a market access in Europe since 2014, has been found to lower the risk of the primary composite cardiovascular outcome and death among Type 2 diabetes patients at high risk for cardiovascular events[5] (Zinman et al. 2015). In Europe, SGLT2 inhibitors are in fact nowadays considered as priority drugs for diabetics at high risk of cardiovascular diseases (Airaksinen 2021). In 2021 they covered over 18 % of all diabetes drug costs in Finland. The share has grown rapidly as it was only 13 % in 2019. (Kelasto 2023.)

Glp-1 analogues have become increasingly common drug among Type 2 diabetics since 2011, when they were added into reimbursement system of Finland (Aaltonen et al. 2018). They have also been shown to reduce the risk of cardiovascular events (Marso et al. 2016). Costs of Glp-1 analogues reached the level of metformin in 2015 being 18 % of the total costs of diabetes drugs. However, metformin was used approximately 12 times more (Aaltonen et al. 2018) indicating that the Glp-1 analogues are relatively expensive. Overall, the share of the costs of metformin dropped from 41 to 8 % over 2003–2021 (Kelasto 2023; Aaltonen et al. 2018).

The cost share of gliptins has also increased rapidly since they were included in the reimbursement system in 2007, being 62 % in 2015 (Aaltonen et al. 2018). However, the share has fallen to 15 % by 2021 as Glp-1 analogues and SGLT2 inhibitors have become more common (Kelasto 2023).

The costs of insulins have increased in the 2000s due to higher numbers of drug purchases and increased quantity of drugs contained per purchase. Also, new insulin groups have been introduced. Especially the new long-acting insulin analogs have become more common. Their share of the total costs for insulins increased from 5 to 74 % over the years 2003–2015. On the other hand, the decrease in their costs over the 2010s associates at least with a decrease in wholesale prices and the introduction of biosimilars, which has led to increased price competition. (Aaltonen et al. 2018; Jauhonen & Sarnola 2020.) However, insulins are not included in generic substitution or reference price system, which partly explains why their prices have decreased more moderately compared with other diabetes drugs (Aaltonen et al. 2018). The Finnish government has proposed that

[5] A composite outcome indicates a list of two or more component outcomes. When any of the events included in the composite outcome is experienced by a patient, it is interpreted as experienced composite outcome. Cardiovascular interventions have been commonly examined using composite outcomes. (Cordoba et al. 2010.)

generic substitution for insulins would be introduced at the beginning of 2024 (Government proposal 314/2022).

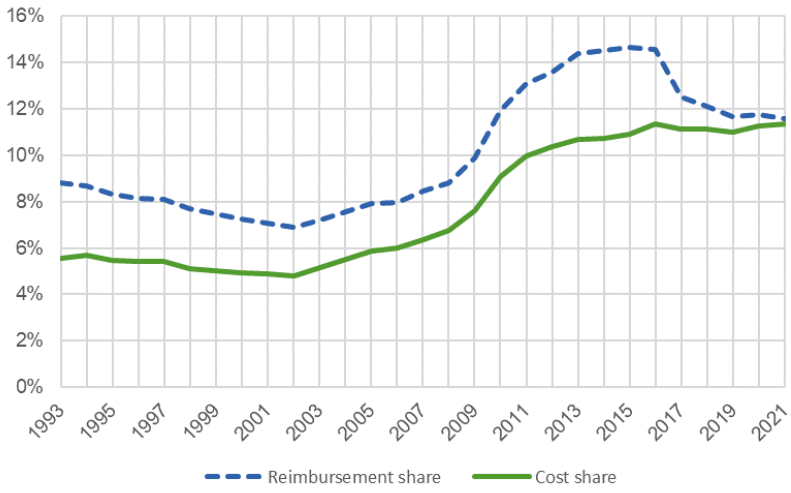

Figure 3: The share of diabetes drug reimbursements and costs in relation to all drug reimbursements and costs. (Kelasto 2023)

Figure 3 displays the share of all diabetes drug reimbursements and costs in relation to all drug reimbursements and costs in Finland. In Figure 3, diabetes drugs refer to both insulins and other antidiabetic drugs. The share of both reimbursements and costs started to increase after 2002, when they were at their lowest during the period considered. The share of costs was over 11 % in 2016. In the same year, the share of reimbursements was over 14 %, respectively. The decrease in the share of reimbursements in 2017 is associated with the reform in which antidiabetic drugs were moved to a lower special reimbursement category (see e.g., Suviranta et al. 2019). Between 2002 and 2016, costs of diabetes drugs have increased more sharply in relation to total drug costs in Finland.

To summarize, diabetes drug costs are significant part of the total drug costs in Finland. In total, they have been continuously growing over the last 30 years. Two main factors for this trend have been the increased number of diabetes patients and the introduction of new, more expensive treatments. The increased number of patients clearly associates with greater total health care costs. However, the impact of new drugs on total health care costs and other indirect costs are more complicated to examine. The total impacts might be negative if the risk of expensive complications of diabetes can be reduced effectively enough. This summarizes one of the most significant challenges of this thesis as well: drug costs cannot be interpreted as a measure of effectiveness of a treatment, or as a direct addition to societal expenses, whether it is about a lifestyle intervention or a new drug.

The treatment might have several other direct or indirect impacts, which in turn might affect the total costs of the treatment. Assessing the cost-effectiveness of a treatment is necessary in order to make rational decisions in health care. The cost-effectiveness of diabetes prevention is discussed in Chapter 4.

4 Is diabetes prevention cost-effective?

4.1 Cost-effectiveness

In addition to economic burden caused by diabetes drug treatment, the disease is associated with considerable health care cost and productivity loss (Jarvala et al. 2010). Moreover, according to studies the cost of the drug treatment, medical care and productivity loss start to rise even before the diagnosis (Nichols et al. 2000; Reini & Honkatukia 2016). Therefore, prevention of the disease among high-risk individuals may appear not only as an improved health but also as improved economic outcomes and cost savings.

The lifestyle intervention implemented in the DPS was shown to reduce the risk of diabetes by 58 % three years after and by 20 % 13 years after the start of the trial. (Lindström et al. 2013; Lindström et al. 2021). Reini & Honkatukia (2016) used these results to study the economic impacts of diabetes prevention. According to their simulations the impact on GDP is over €2 billion in the scenario where 58 % of individuals at high risk of diabetes manage to avoid the disease. In the longer-term scenario where 20 % of the individuals avoided the disease, the positive impact on GDP would be around €743 million. At that time the results indicated over one and nearly 0.4 % of the total GDP of Finland. The growth would be mostly driven by increased labour supply (Reini & Honkatukia 2016)[6]. At this point, one might ask if the growth in the GDP illustrated by Reini & Honkatukia (2016) is cost-effective. How much would it cost to implement an intervention leading this significant decrease in the incidence of diabetes? Would the utility received from the intervention exceed the costs?

Cost-effectiveness analysis aims to estimate the expenses associated with a specific measure of health improvement (Eisman et al. 2020, 3). These analyses are usually based on comparison of treatment cost per quality adjusted life years (QALY) gained as health outcomes. According to theory, QALYs can be applied widely across different health conditions. (Cohen & Reynolds 2008, 3) The quality-of-life is determined by the health

[6] The simulation approach of Reini and Honkatukia (2016) is not entirely unproblematic. They used person-years lost due to early retirements of diabetics as a measure of productivity loss. These estimations were based on the study of Jarvala et al. (2010) and the statistics of Kela. Productivity costs were calculated by multiplying the person-years lost with the median wage in 2014 provided by Statistics Finland. However, no studies have presented the impacts of the DPS-intervention on productivity at an individual level.

utility score, which takes a value between 0.0 and 1.0 depending on level of one's health. A value of 1.0 indicates perfect health whereas 0.0 is interpreted as equivalent to death. (Herman 2015, 3.) QALYs are calculated by multiplying the health utility score by time (typically years) a person has spent in the condition the utility score indicates and summing these quality adjusted life years over time (Cohen & Reynolds 2008, 4).

Interpreting and applying of cost-effectiveness analyses, however, is not entirely unproblematic. For instance, QALYs can be derived with various, direct and indirect, methods which may make comparisons of different studies inaccurate[7]. Especially health utilities, representing the strength of preferences for a health state, are likely to vary depending on the method, measure or subjects examined, as well as discount rates used to estimate the current value of health (and costs) accumulated in the future. (Shields & Elvidge 2020, 3.) In addition, cost-effectiveness ratios can seriously differ as the time horizon of an analysis is changed[8]. Hence, the time horizon considered should be long enough to detect all the effects of an intervention on health and economic outcomes. (Cohen & Reynolds 2008, 4.) However, another challenge in QALY approach is that even over a long study period it might be difficult to capture all the effects of an intervention, such as spillover effects on family members (Whitehead & Ali 2010, 17).

Lindgren et al. (2007) simulated the 6 years cost-effectiveness of the DPS-intervention using the Swedish cohort as the object of the study. The cohort consists of every third 60 year old individuals that have been randomly selected from the residents of Stockholm County. a random sample of every third 60-year-old resident living in Stockholm County (The cohort of 60-year-old men and women 2012). Lindgren et al. (2007, 180) extracted subjects from this cohort into their simulations based on the inclusion criteria of DPS. In their simulation model the intervention was assumed to affect the risk of diabetes and cardiovascular diseases. The risk and treatment costs of these diseases were derived from

[7] Direct methods include for instance time trade of methods and non-preference-based visual analogue scale. Indirect methods indicate applying of preference weights collected from generic or disease-specific measures (e.g., EuroQoL-5D or the health utilities Index). (Shields & Elvidge 2020, 3.)

[8] Incremental cost-effectiveness ratio = $\frac{Cost_{New} - Cost_{Reference}}{Effectiveness_{New} - Effectiveness_{Reference}}$

earlier studies[9]. QALYs gained were calculated using utility weights estimated with EQ-5D[10] instrument by Clarke et al. (2002). (Lindgren et al. 2007, 179.)

Lindgren et al. (2007, 180) found the lifestyle intervention program among the Swedish cohort to be cost saving from the perspective of the health care payer. According to their simulation the mean total cost discounted by 3 percent was €18.212 in the intervention group and €20.065 in the control group, indicating savings of €1.853. These costs included costs of the intervention and other direct costs, as well as indirect costs such as work absences. QALYs gained were 12.50 in the intervention group and 12.30 in the control group, respectively. However, the savings might be overestimated since all treatment costs of diabetics were included, whether or not caused by diabetes. On the other hand, the QALYs might be underestimated since only two health states related to cardiovascular diseases are being considered. Hence, only part of higher mortality of patients with diabetes is captured through these simulated risks of MI and stroke. (Lindgren et al. 2007, 181.) In addition, standard deviations reported are large, indicating remarkable variation in the possible results. Moreover, participation rate of 67.5 % assumed by Lindgren et al (2007) is relatively high. For instance, in Finnish national prevention program, FIN-D2D, the participation rate was only 38.2 % (Saaristo et al. 2010).

Diabetes Prevention Program Research Group (2012) examined the 10 years cost-effectiveness of the Outcomes Study (DPPOS)[11] of The Diabetes Prevention Program (DPP). Instead of modelling the cost-effectiveness for a simulated cohort like Lindgren et al. (2007), they analysed the actual costs observed from DPP participants. DPP was a randomized, controlled trial carried out in the U.S. It was relatively similar in terms of objectives, intervention and implementation compared with the DPS; the goal was to find out if Type 2 diabetes could be delayed or prevented among middle-aged high-risk

[9] The risk of developing diabetes was derived from DPS and the cost of treatment and microvascular complications was estimated using the results of Henriksson et al. (2000). The risk of myocardial infarction (MI) and stroke was in turn based on the study carried out in UK by Kothari et al. (2002). Direct and indirect costs associating with these cardiovascular diseases were taken from the studies of Zethraeus et al. (1999) and Johannesson (2001). The cost of the intervention was estimated using data from Stockholm County Council. (Lindgren et al. 2007, 179.)

[10] EQ-5D is a questionnaire used to measure health status. It includes qualitative measures for mobility, usual activity, self-care, pain/discomfort, depression, and anxiety, as well as quantitative measures of health outcome (visual analogue scale from patient's self-assessment). (Clarke et al. 2002, 341.)

[11] DPPOS is in practice a follow-up study of DPP participants. It aims to examine long-term effects of the interventions on health and development of diabetes. (The Diabetes Prevention Program Research Group 2012.)

individuals by improved dietary and physical activity.[12] However, in DPP a part of the study cohort not included in the intervention group received a medication intervention which meant either metformin or placebo. (Herman 2015.) According to The Diabetes Prevention Program Research Group (2003), the incidence of diabetes over 3 years was 58 and 31 % lower in the intervention and metformin group, compared with the placebo group. After additional 7 years of follow-up, respective numbers were 34 and 18 % (Diabetes Prevention Program Research Group 2009). The 10-year cumulative undiscounted direct average medical cost were slightly larger for the intervention group ($31,382) compared with the placebo group ($29,759), and lowest for the metformin group ($29,665). Direct non-medical cost was on average $143,504 for the metformin group, $146,930 for the intervention group and $146,124 for the placebo group.[13] Significant differences in indirect costs were not found. (The Diabetes Prevention Program Research Group 2012.)

Outcomes were measured as QALYs using Self-Administered Quality of Well-Being Index (QWB-SA[14]) in assessing health utilities. According to The Diabetes Prevention Program Research Group (2012) the cumulative 10-years per capita QALYs were 6.89, 6.79 and 6.74 for the intervention, metformin, and placebo groups. After 3 percent discount, lifestyle intervention cost $12,878 per QALY compared with placebo. The intervention cost around $15,000 per QALY compared with metformin, respectively. Metformin intervention was in turn less expensive and produced close to same health outcomes compared with placebo. Conclusion of the study was that the lifestyle intervention is cost-effective and metformin intervention might be even cost saving. (The Diabetes Prevention Program Research Group 2012.)

Comparing the results of Lindgren et al. (2007) and The Diabetes Prevention Program Research Group (2012) is challenging for at least three reasons. First, different measures, EQ-5D by Lindgren et al. (2007) and QWB-SA by The Diabetes Prevention Program

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[12] Inclusion criteria followed similar pattern as in DPS enrolling individuals with glucose intolerance and body mass index at least of 24 kg/m2 (Herman 2015). The main goal for the intervention group was as well similar; to reduce body weight at least 7 per cent of initial body weight (The Diabetes Prevention Program Research Group 2002).

[13] Direct medical costs were calculated by estimating resources used during the interventions and are standard for each participant (Diabetes Prevention Program Research Group 2003). Outside the study costs and indirect costs were calculated from case report forms and surveys collected annually from participants. (Herman 2015.)

[14] QWB-SA is a utility model providing health utility score by combining preference weighted values of symptoms (The Diabetes Prevention Program Research Group 2012).

Research Group (2012), are being used to determine health utility scores, which might affect the resulted QALYs. Second, time periods differ between the studies which might lead to different cost-effectiveness ratios. More optimistic results of Lindgren et al. (2007) may partly be attributed to the shorter period, since the effectiveness of diabetes prevention has been found to diminish over time (see e.g., Lindström et al. 2021). Third, Lindgren et al. (2007) simulated the effects in the Swedish cohort consisting of 60-year-olds, whereas The Diabetes Prevention Program Research Group (2012) examined on average 51-year-old American DPP-subjects in a trial-based study. The effectiveness of diabetes prevention has been found to be age dependent (Lindström et al. 2021), which may impact on the QALYs. Indeed, the effects might vary depending on the target population. Considering that results of cost-effectiveness studies might generally vary significantly depending on these factors mentioned, these results should be treated with caution.

Both studies are based on randomized controlled trials. Diabetes prevention and its effects are modelled according to DPS in the study of Lindgren et al. (2007), and DPP-participants are examined in the calculations of The Diabetes Prevention Program Research Group (2012). Therefore, the external validity of the results could be questioned. In other words, it could be asked whether they can be generalised on, for instance, younger population. Lindström et al. (2008) found that DPS was most effective among the oldest participants. Hence, one could argue that perhaps the prevention is not effective among individuals under middle age. In the context of policy making, following question could be asked concerning cost-effective studies: how well do they illustrate the costs-effectiveness of diabetes prevention in general? Is the prevention cost-effective outside the controlled experimental environment? These questions are discussed in more detail in Chapter 4.2.

When interpreting cost-effectiveness analyses, it should be also noted that no explicit threshold exists to define whether the treatment is cost-effective or not (Cohen & Reynolds 2008, 2). Thus, interpretations partly depend on willingness to pay. In fact, thresholds used vary widely across countries. For example, within the U.S. the threshold recommended by the Institute for Clinical and Economic Review (2020, 71) ranges from $50,000 to $200,000 per QALY gained. In England and Wales an appropriate threshold is set between £20,000 and £30,000 per QALY gained by the National Institute for Health and Care Excellence (2012, 123). In Finland, there is no general recommendation for the

threshold of cost-effectiveness (Jit et al. 2009, 6122). However, according to World Health Organisation (WHO) the cost-effective ratio up to three times per capita GDP of a country is cost-effective. Moreover, the ratio up to annual per capita GDP is considered as “very cost effective”. (Tan-Torres Edejer et al. 2003, 245.)

In addition to DPS and DPP, several other studies around the world have examined the cost-effectiveness of diabetes prevention. Sathish et al. (2020) aimed to extrapolate the results of earlier studies from high-income countries to low- and middle-income countries. They examine the cost effectiveness of randomized controlled trial in India. They found the community-based peer-support prevention to be cost-effective. However, they do not report the participation rate which in the context of larger implementation would likely affect the effectiveness of the intervention (see e.g., Galaviz et al. 2018, 1532). In addition, period considered is only two years. As the preventative effect of lifestyle interventions has been observed to decrease over time (Lindström et al. 2013; Diabetes Prevention Program Research Group 2009), and as the absolute risk reduction reported by Sathish et al. (2020) is quite small (2.1%), it could be questioned if the intervention is cost-effective in the longer term.

Neumann et al. (2011) simulated a hypothetical intervention programme in Germany using results from earlier diabetes prevention studies and programmes. They found prevention interventions to be potentially cost-effective. However, they report wide level of uncertainty in their results. Moreover, they assume the participation time to be five years for all subjects which might be unrealistically high in clinical practise.

In addition to RCTs, one diabetes prevention related cost-effectiveness study based on quasi-experiment was identified. Johansson et al. (2009) found the results of 10-year intervention implemented in three municipalities in Swedish quasi-experiment to be favourable only among women in two intervention areas. This might, according to Johansson et al. (2009), be due to the differences in implementation strategies between the municipalities. Based on sensitivity analysis, however, reported QALYs are uncertain. Moreover, Johansson et al. (2009) do not display any pre trends of the control municipalities that were selected based on geographical and demographical factors. Hence, it remains unclear whether the intervention and control groups are comparable and similar enough in terms of, for instance, diabetes incidence before the experiment.

Indeed, several promising or at least neutral results have been obtained from studies examining the cost-effectiveness of diabetes prevention. However, wide range of methods, assumptions and time periods have been considered in these studies, leading to different results. In view of this uncertainty, cost-effectiveness analyses need to be interpreted critically. Thus, drawing certain conclusions for at least following questions is difficult: What kind of intervention is cost-effective in the "real world"? Which assumptions should we make when assessing the impact of an intervention, in order to scale the effects accurately enough? Challenges in scaling up interventions to the real world are discussed in the next section.

4.2 Scaling up interventions

When planning an implementation of an intervention program as part of the national healthcare, the limitations of cost-effective analyses should be considered. While clinical trials are generally covered with valid data to examine, significant differences for instance in terms of patient selection or clinical factors might exist compared to the real world (Cohen & Reynolds 2008, 4). These differences may not be fully taken into account in cost-effectiveness analyses.

Participation rate and patients' adherence to the intervention are one of the most significant concerns when planning the implementation. Icks et al. (2007, 474), for instance, argue that patients' participation rate assumed in previous cost-effectiveness studies has been unrealistically high, leading to excessive cost-effectiveness ratios. This scenario is natural, since according to Galaviz et al. (2018, 1532) patient's adherence to the interventions has significantly affected the effectiveness of these interventions. As no one can be forced to participate, the participation rate might remain low, making a large-scale implemented intervention potentially inefficient.

On the other hand, even though the participation rate was high at the start of the intervention, poor adherence by the participants might decrease the effectiveness of the intervention. This is crucial as a part of direct costs of the intervention probably remain the same even if participants poorly adhere to, for example, dietary or exercise programs. Implementing a large-scale intervention in national health care likely involves costs that are not directly related to adherence or participation rate. In other words, costs that arise regardless of the number of individuals actively participating in the intervention. These could include, for instance, administrative costs, program development costs,

collaboration costs with various stakeholders such as healthcare organizations and policy makers, organizational costs, equipment costs, recruitment and educational costs of health care professionals, research and evaluation costs, and so on (see e.g., Sohn et al. 2020).

Patient selection is another important factor when assessing economic outcomes (Cohen & Reynolds 2008, 4). Since participation is voluntary, only individuals who are particularly motivated to improve their lifestyles may participate. For instance, the dropout rate was low in DPS, which might be due to the opportunity to visit nurse and doctor annually and to receive measurement data from the tests conducted during the intervention (Lindström et al. 2021). Another possible explanation is that individuals with higher motivation to improve their lifestyles compared with other high-risk individuals, have been selected for the trial. This might hinder the generalizability of the results when considering the scale-up to a larger and more diverse target population. Additionally, since the participants of DPS were selected only from five relatively large Finnish cities (Uusitupa et al. 2000, 137), the results may not be generalizable to more remote areas. For instance, disparities in recourses, populations, and preferences of stakeholders may impact the effectiveness (Brown et al. 2022, 2). When scaled-up, the effectiveness of the intervention might indeed vary when implemented among the wider study population, in a different environment (Milat et al. 2013). Thus, generalizing the results from controlled trials to a real-word context may be challenging.

Even though economic theory provides indications of economies of scale, additional costs compared to a clinical trial may arise when implementing a larger scale intervention (Milat et al. 2013, 291–292). For instance, additional time is required for supporting intervention delivery to a greater number of participants, as well as for intervention content development and updates to maintain evidence-based efficacy (Brown et al. 2022, 10). Moreover, to ensure suitability and applicability of the intervention within a specific context and target population, additional resources may be needed for tailoring interventions. (Eisman et al. 2020, 8–9).

Despite the several challenges in evaluating the scalability, studies implemented in a smaller scale are still important when planning and simulating the implementation to a larger scale. According to Milat et al. (2013, 289), the efficiency observed in a smaller scale is necessity for broader implementation. In addition, Neumann et al. (2011) argue that it is even unethical to wait until data from larger interventions exists to draw

conclusions about the cost-effectiveness of diabetes prevention. On the other hand, it has also been stated that process evaluation of quasi and natural experiments implemented in real world should be utilized more. An advantage of systematic process evaluation is that it allows for the withdrawing of the funds if the goals of the intervention are not reached. (Milat et al. 2013, 292–295.)

From the perspective of a policy maker, allocating scarce resources to a specific intervention always creates an opportunity cost. There are several other areas where the resources could be used and allocating them to one option means giving up on another. Therefore, even if an intervention is shown to be cost-effective, it may not necessarily guide the decision-maker to implement it directly as there may be other possible acts that are at least as effective and feasible. However, the decision-maker never has perfect data available to guide decision-making (Milat et al. 2013, 295). Excessive delay in implementation can indeed become costly, especially in the context of a disease like Type 2 diabetes. Therefore, it might be reasonable to implement experiments in the national healthcare even when complete certainty about the cost-effectiveness is lacking, but indeed ensuring systematic process evaluation.

For instance, FIN-D2D, that was part of the world's first national prevention and treatment development programme (DEHKO), was implemented in 2003-2007 in five hospital districts of Finland. The aim was to develop the identification of high diabetes risk individuals and to review and improve life-style counselling in primary health care. Overall, 38.2% of 10,149 people participated in one year follow up, of which 68% took part in at least one intervention visit. In case of 5% weight loss, which was reached by nearly one fifth of the participants, the diabetes risk was reduced by 69% compared with the subjects whose weight remained unchanged. (Saaristo et al. 2010.) However, no studies have examined the cost-effectiveness of the FIN-D2D.

The StopDia study, also carried out in Finland, was the first wide-ranging randomized controlled trial that considered combined digital and group-based interventions in primary health care. Overall, 2907 adults were randomized either into a digital lifestyle intervention, combination of digital and group-based lifestyle intervention or a control group. According to the results, the combined intervention improved diet quality and reduced truncal obesity as well as hindered the development of insulin resistance. Active

participation was found to improve the results (Lakka et al. 2023). No process evaluations about the cost-effectiveness of the StopDia are available.

In recent decades, Finland has clearly been one of the leading countries in the research of diabetes prevention. However, relatively little is still known about the cost-effectiveness of "real life" implementations of preventive interventions, and significant differences exist between studies. As the economic burden of diabetes has been constantly growing, interventions, such as in the StopDia and FIN-D2D, are likely to be subjects of increasing economic research in the future. Developing process evaluation in terms of cost-effectiveness is crucial in order to determine the rationality of these interventions from both public health and economic perspectives.

5 The impact of diabetes prevention on drug costs

5.1 Data and methods

To examine the impact of diabetes prevention on drug costs, I use the data from the DPS. The DPS-data contains, in addition to baseline health measurements and indicators for gender, socioeconomic status and education, individual drug purchases (Social Insurance Institution of Finland) from 1993 to 2021. Each purchase is classified by international ATC codes. I use this classification to analyse the effect of the intervention within drug groups. The groups analysed in this thesis are diabetes drugs (A10) and cardiovascular disease drugs (C).

The baseline characteristics of DPS participants are shown in Table 1. Altogether, over two thirds of the initial participants were women. In schooling there was no big differences at baseline, except that university degree was little more common in the intervention group, whereas high school degree tended to be more common in the control group. Most of the participants were married but, however, little more commonly in the control group. The baseline health characteristics were on average very similar between the groups regarding both means and standard deviations, except systolic blood pressure, which appeared to be slightly higher in the intervention group.

Dropout rate was relatively low as only eight percent of participants dropped out during the intervention (Lindström et al. 2021). However, during the period of 19 years examined in this thesis, 75 participants died, 39 in the intervention group and 36 in the control group. These participants were removed from the sample after the year of their death. Thus, the sample is unbalanced and contains data from participants who were alive at the start of the year considered.[15]

[15] Initially, 522 participants took part in DPS. As shown in Table 1, the data I analyse contains only 505 participants. The remaining 17 individuals have refused to allow the linking of their DPS-data with the register data.

Table 1: Baseline Characteristics

Baseline Characteristics			
	Intervention (N=257)	Control (N=248)	Overall (N=505)
Age (years)			
Mean (SD)	55.4 (±7.30)	55.0 (± 6.92)	55.2 (± 7.11)
Sex			
Male	88 (34.2%)	78 (31.5%)	166 (32.9%)
Female	169 (65.8%)	170 (68.5%)	339 (67.1%)
School			
University degree	34 (13.2%)	20 (8.1%)	54 (10.7%)
Vocational school	71 (27.6%)	69 (27.8%)	140 (27.7%)
Elementary school	99 (38.5%)	98 (39.5%)	197 (39.0%)
High school and/or college	52 (20.2%)	61 (24.6%)	113 (22.4%)
Marital			
Divorced	26 (10.1%)	24 (9.7%)	50 (9.9%)
Widow/Widower	20 (7.8%)	12 (4.8%)	32 (6.3%)
Unmarried	19 (7.4%)	16 (6.5%)	35 (6.9%)
Married	191 (74.3%)	196 (79.0%)	387 (76.6%)
Body Mass Index			
Mean (SD)	31.4 (± 4.59)	31.2 (± 4.51)	31.3 (± 4.55)
2H-glucose (mmol/l)			
Mean (SD)	8.88 (± 1.52)	8.90 (± 1.46)	8.89 (± 1.49)
HbA1c (mmol/l)			
Mean (SD)	38.3 (± 6.28)	37.6 (± 6.30)	38.0 (± 6.29)
Diastolic blood pressure			
Mean (SD)	85.7 (± 9.41)	85.6 (± 9.99)	85.7 (± 9.69)
Systolic blood pressure			
Mean (SD)	140 (± 17.7)	136 (± 17.4)	138 (± 17.6)
High density lipoprotein			
Mean (SD)	1.21 (± 0.308)	1.22 (± 0.277)	1.21 (± 0.293)
Low density lipoprotein			
Mean (SD)	3.64 (± 0.840)	3.59 (± 0.811)	3.61 (± 0.826)

Overall, the differences between the groups are small as assumed since the groups have been randomly assigned. This is, by randomizing participants into the groups one can assume the selection bias to be zero (Angrist & Pischke 2008, 12–16). Therefore, the groups considered are very similar and well comparable. However, slight differences between the groups exist. In addition, as the follow-up period is this long, advantage of the initial randomization does not necessarily hold completely in late years. Dropouts and deaths might have violated the balance between the groups. Adjusting the estimation with baseline controls might precise the results. However, fixed effects can be used to reduce

confounding effect of time-invariant factors that are unobserved by the baseline measurements (Gunasekara et al. 2014). In the fixed effect model, these unobserved factors are controlled through coefficients of dummies for each individual. Additionally, unobserved time-specific effects, that are the same for all individuals, can be controlled through coefficient for each time dummies. (Angrist & Pischke 2008, 166.) The estimator accounting for both individual and time fixed effects is usually called two-way fixed effects estimator (Wooldridge 2021, 2). To examine the effects of the lifestyle intervention, I estimate the following two-way fixed effect model:

$$y_{itr} = \delta_i + \lambda_t + \sum_{r=1}^{19} \beta_r LI_{ir} + \varepsilon_{itr}, \quad (1)$$

where y_{itr} is the drug cost for participant i, observed in year t and r years after the start of the intervention, δ_i is the individual fixed effect, λ_t is the year fixed effect, β_r is the regression coefficient for the indicator LI_{ir} which is equal to 1 for an individual in the lifestyle intervention group and ε_{itr} is the error term. Terms LI_{ir} are the interactions between the intervention status and the variable for relative time. Relative time indicates the number of years from the beginning of the intervention. The individual fixed effect δ_i controls the effect of all time invariant factors, such as the effect of genes. Instead, the year fixed effect λ_t controls the effect of time variant factors, such as macro-economic shocks, that are the same for each participant.

In RCTs, even though selection or confounding bias should not be a concern, fixed effects can be used to increase statistical efficiency (Alison 2009). To demonstrate this, I also present the results for pooled ordinary least squares (OLS) regression without fixed effects, but instead including the baseline characteristics as controls. Simply, this model estimates annual differences between group level averages adjusted with baseline covariates and ignores individual specific effects. In this thesis, pooled OLS is also used to visualize the predicted group level average cost developments. I estimate the following pooled OLS model:

$$y_{itr} = \alpha_t + \sum_{r=1}^{19} \beta_r LI_{ir} + \gamma_t X_i + \varepsilon_{itr}, \quad (2)$$

where y_{itr} is the drug cost for participant i in year t and observed r years after the beginning of the intervention, α_t is an intercept which is assumed to be constant, β_r is the regression coefficient for the lifestyle intervention indicator LI_{ir} and ε_{itr} is the error term.

In addition, γ_t is the coefficient for the X_i which includes the set of controls for health variables measured at baseline as well as variables for gender and age[16].

To make results of the Model (1) more understandable, I first visualize the marginal cost developments over time derived from the Model (2)[17]. Since logarithmic transformation for a cost variable containing a high number of zeros is not appropriate, interpretations of the percentage difference cannot be made based on the estimates of Model (1). Hence, visual presentation of the predicted cost developments puts the observed differences into a perspective. Next, I present the estimates for the annual average differences in drug costs obtained from Model (1). The results for average cumulative drug costs are presented similarly. The same approach is used for each drug class considered in this thesis.

I start by analyzing the impacts of the intervention on total drug costs. This method is applied for two reasons. First, the average consumption of all drugs should intuitively correlate negatively with health, at least in the long term. In the shorter period, non-serious short-term illnesses may raise drug costs temporarily. As summarized in Chapter 2.4, the results of DPS indicate that the intervention had on average positive impacts on individuals' health by lowering the risk of Type 2 diabetes. Therefore, it is appropriate to assume that the overall consumption of drugs would be lower in the intervention group over the years followed up. Second, the overall experience about the total drug consumption of the study groups puts the later observed differences into a perspective.

Next, I move to examine if the observed differences between the groups differ between certain drug groups. The groups I analyze in this thesis are diabetes drugs (A10) and cardiovascular drugs (C). Diabetes drugs include insulins (A10A), antidiabetic drugs (A10B) and other diabetes drugs (A10X). As summarized in Chapter 2.4, the preventive effect of the intervention was observed to maintain at least for 13 years. In Chinese Da Qing study, lifestyle interventions were found to delay the onset of diabetes and reduce cardiovascular disease events and deaths during 30-year follow-up (Gong et al. 2019). However, in 2017 the reimbursement rate of antidiabetic drugs (A10B) was dropped from

[16] Since the data is this small, only health characteristics which were observed for each individual, are included in model (2). Selected health variables are BMI and two-hours glucose level. In the model comparison, education and marital status were excluded from the final model. This is natural, since according to Lindström et al. (2008), the effect of the intervention was independent of them.
[17] Predictions of the pooled group averages were derived using the R package 'ggeffects', developed by Lüdecke (2018).

100 to 65 percent (Government proposal 184/2016). This reform might complicate the interpretations of the impacts of the intervention. Thus, I limit the examination period to 19 years as this is the point when participants who started the intervention in 1998 have completed the year before the reform year.

Health care expenditure data is usually skewed and contains zero values (Cantoni & Ronchetti 2006, 198; Deb & Norton 2018, 494–495). This holds also for the data I analyze. Both Models (1) and (2) estimate differences in average costs without any transformation. Hence, the limitation of Models (1) and (2) is that the estimates might be misleading in case of extreme values and large variances in the outcome. Two-part models are commonly used for health care data to deal with these special characteristics (Mihaylova et al 2010, 903; Deb and Norton 2018). Therefore, I use two-part model as an alternative method to examine cumulative drug costs. In the first part of the model, I estimate the probability that a participant has any drug costs over the period of 19 years using a logit model for the full sample. In the second part, I estimate a generalized linear model (GLM) with natural logarithm as a link function using data for participants who have any drug costs over 19 years.[18] The results of the two-part model are not completely comparable with the results of Model (1), especially regarding the second part where the sample is limited to those with any costs. However, alternative approach is used as a tool to consider the robustness of the main results. The results for the alternative two-part models are presented in Appendix 4.

5.2 Total drug costs

I start the analysis by examining the effect of the intervention on total drug costs. Both prescription drugs and over-the-counter drugs are included. The effect on annual average costs is examined first. The regression coefficients for both Models (1) and (2) are presented in Table A.1. of Appendix 1[19]. In Table A.1., each coefficient is the interaction between lifestyle intervention variable LI and relative time and represents the effect of the intervention on total drug costs at particular point of relative time. Model (1) is

[18] For the second part, Park test was used to determine the distribution family, as suggested by Deb and Norton (2018, 497). On this basis, Gamma distribution was considered as the most appropriate distribution. For total drug costs only the second part was modeled since there were not any participants with zero cumulative costs at the end of the follow-up.

[19] All the regression tables in Appendices 1, 2, 3 and 4 were made with R package ‘stargazer’ by Hlavac (2022).

adjusted with two-way fixed effects, whereas Model (2) estimates the coefficients for pooled OLS adjusted with baseline controls. The costs have been converted into 2021 currency by the cost-of-living index (Consumer price index 2022) reported by Statistics Finland.

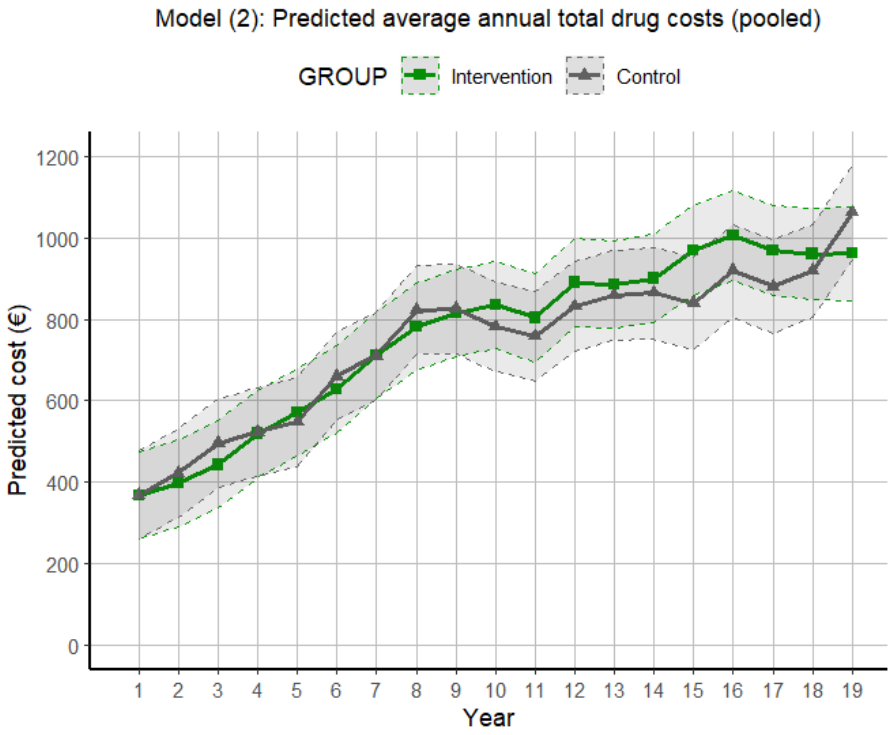

Figure 4: Predicted average annual total drug costs (pooled)

Figure 4 displays the predicted average cost developments over time derived from pooled Model (2)[20]. Confidence intervals are presented at the level of 95%. According to Figure 4, costs within all drugs did not differ remarkably between the groups until year 10, in which the intervention group experienced a slight increase in average costs compared with the control group ($p>0.05$). At this point, total drug costs were on average around €800 for both groups. Compared with the control group, the average costs remained slightly higher for the intervention group until year 19. In year 19, average costs were slightly under €1000 for the intervention group and slightly over €1000 for the control group. However, coefficients derived from Model (2) are not statistically significant as shown in Table A.1.

Figure 5 displays the coefficients of Model (1) presented in Table A.1. Confidence intervals are shown at the level of 95%. Compared with Model (2), Model (1) shows the

[20] R package 'ggeffects', developed by Lüdecke (2018), was used to plot the marginal cost developments of the groups.

effect of similar size. The differences were small over the first years. In year 10, average costs were around €61 ($p>0.05$) higher for the intervention group. The difference was at its highest in year 15, in which the intervention group had around €147 ($p<0.1$) higher average costs. In the 19th year, the average costs of the intervention group were around €99 ($p>0.05$) lower, compared with the control group. However, confidence intervals are relatively large and statistically significant differences are not observed at the level of five percent. Therefore, the results are uncertain and indicate that there might be a wide range of possible values for the true coefficients.

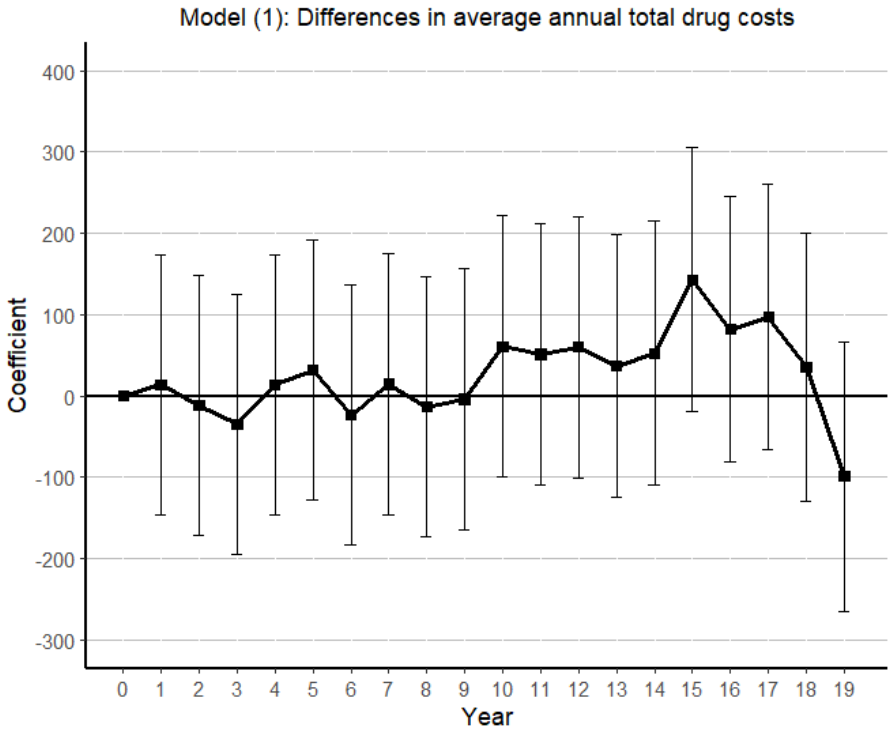

Figure 5: Differences in average annual total drug costs

It could be argued that the intervention may have improved the drug adherence of the intervention participants, and thus also raised their drug costs. However, this would intuitively have been expected to appear rather in early years of the follow-up particularly, since the active lifestyle guidance lasted on average for four years. On the other hand, improved health in the intervention group over the first years may have been impacting negatively on drug costs, despite the potentially better adherence. Compared with the control group, late years increase in the average costs of the intervention group might also be attributed to frequent doctor visits during the intervention, which may have lowered participants' threshold to seek medical attention in later years. This may have affected

significantly on drug consumption over the late years as participants were on average 65 years old at the middle of the follow-up, and hence, at great risk of long-term illnesses.

Moreover, diabetes diagnosis itself can be experienced as a certain kind of information shock. Hence, the diagnosis might affect health behaviour and thus the measured effect of the intervention. For instance, Gaggero et al. (2022) found that weight reduction is greater shortly and up to three years after the diabetes diagnosis. During the DPS, the control group received significantly more diagnoses (Lindström 2003, 3234). Hence, the control group has been exposed to a higher number of these information shocks. This might have reduced the effect of the intervention on health if individuals in the control group have improved their lifestyles due to the diagnoses. This in turn may have had negative effects on drug consumption and costs for the control group.

Coefficients for differences in average cumulative total drug costs are presented in Table A.2., in Appendix 1. Similarly, coefficients are shown separately for Models (1) and (2). Predicted cumulative average drug costs derived from the Model (2) are displayed in Figure 6. Confidence intervals are presented at the level of 95%. Each point represents average cumulative costs of participants involved from year 1 to the year examined. This indicates that if a participant drops out from the study or dies in year t, his or her cumulative costs from years 1 to t are no longer involved in the calculation in year t+1. Throughout the 19-year follow up, the average cumulative total drug costs were nearly €14.000 for the intervention group and slightly over €13.000 for the control group. However, coefficients of the Model (2) are not statistically significant.

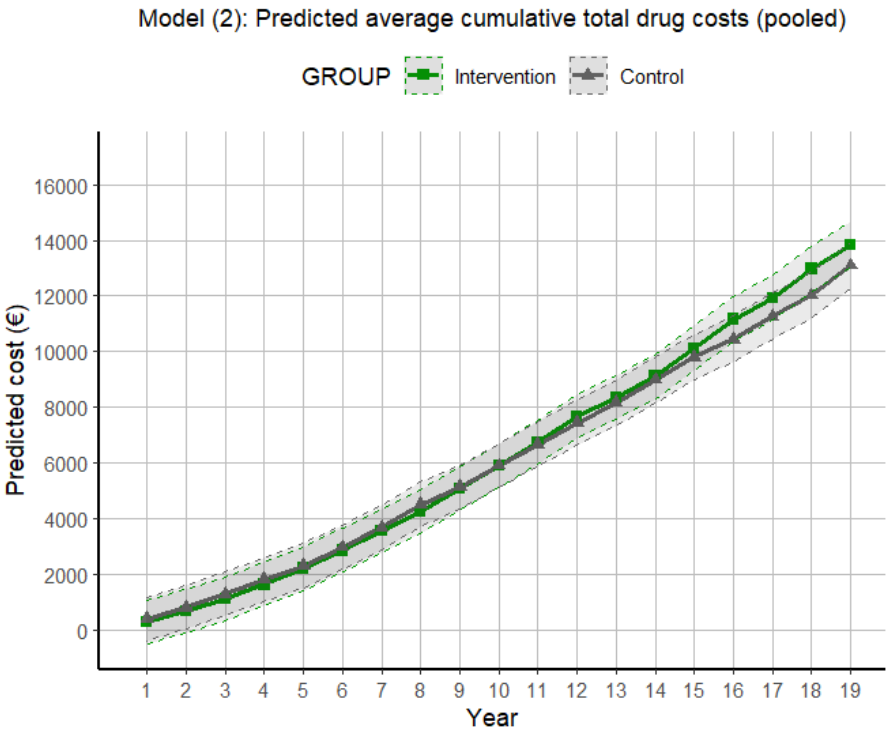

Figure 6: Predicted average cumulative total drug costs (pooled)

Figure 7 shows the coefficients obtained from Model (1), which represent the annual differences in average cumulative costs. Confidence intervals are displayed at the level of 95 %. The differences were negligible over the first nine years. Throughout the 19-year period, the cumulative drug costs were on average €736 ($p>0.05$) higher in the intervention group compared with the control group. However, coefficients of the Model (1) are not statistically significant.

Table A.7., which is presented in Appendix 4, shows the results for alternative two-part model. In the case of all drugs, only second GLM-part is estimated since there was not any participant with zero total drug costs at the end of the follow up. Hence, the logit model, which shows to difference in odds of having any costs, cannot be estimated. The GLM estimates the relative difference in average cumulative total drug cost throughout the 19-year follow up. According to the Table A.7., the intervention group had on average 7 % higher cumulative total drug costs. Neither this is statistically significant. However, this is in line with the result derived from Model (1).

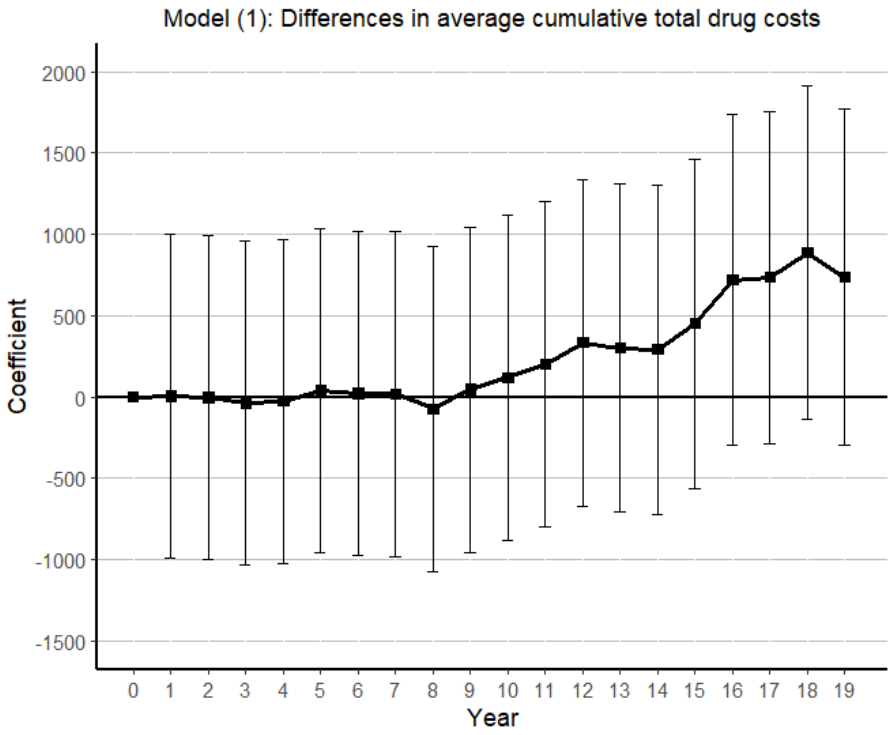

Figure 7: Differences in average cumulative total drug costs

5.3 Diabetes drug costs

In this subchapter, I examine the effects of the DPS intervention on diabetes drug costs. The drug group considered includes drug purchases containing the ATC code A10. The class A10 consists of insulins (A10A), antidiabetic drugs (A10B) and other diabetes drugs (A10X). The impact on average annual diabetes drug costs is examined first. The coefficients for Models (1) and (2) are presented in Table A.3. of Appendix 2. Each coefficient is the interaction between the intervention status LI and relative time and represents the impact of the intervention on diabetes drug costs at considered time point. The cost-of-living index (Consumer price index 2022) has been used to convert the costs into 2021 currency.

Figure 8 displays the predicted average cost development of both groups over time derived from Model (2), the diabetes drug costs as an outcome. The confidence intervals are presented at a level of 95%. Obviously, costs within diabetes drugs were minimal during the first years since the participants had not yet been diagnosed with diabetes at the start of the trial. Moreover, the incidence of diabetes was relatively small during the first years as there were 27 (11%) diabetes cases in the intervention group and 59 (23%) in the control group during first four years (Tuomilehto et al. 2001). According to Figure

8, the average annual diabetes drug costs remained at the lower level for the intervention group over the whole follow up period, compared with the control group. In year 19, annual diabetes drug costs were on average around €325 and nearly €410 for the intervention and control groups. However, coefficients obtained from Model (2) are not significant at the level of five percent.

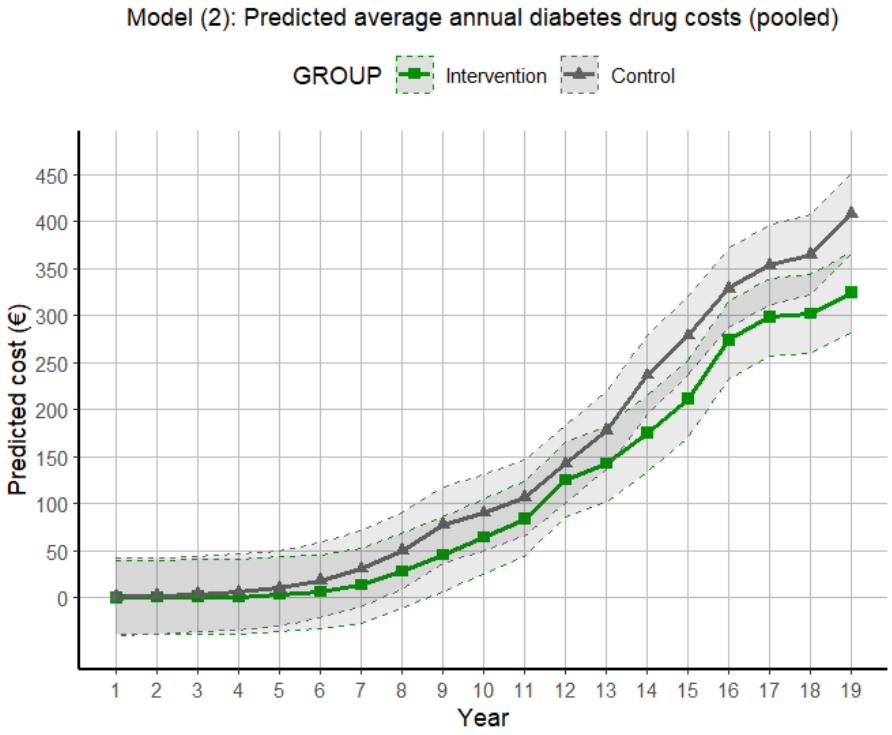

Figure 8: Predicted average annual diabetes drug costs (pooled)

Figure 9 displays the coefficients of Model (1), shown in Table A.1. The impacts of similar size are observed with the Model (1), compared with Model (2). However, slightly better statistical efficiency is gained by the Model (1) with two-way fixed effects. According to Figure 9, the difference between the groups increased over the first nine years. However, these differences are not statistically significant. After year 9 the level of the difference decreased over the next three years. Over the last seven years, participants in the intervention group had on average €54 lower costs annually, compared with the control group. The difference reached its maximum at year 19, when the intervention group had on average €72 ($p<0.05$) lower costs over the year. On average, the intervention group had €28 lower annual costs over the whole 19 years follow-up. However, the confidence intervals are wide, and only the difference for year 19 is statistically significant at the level of five percent.

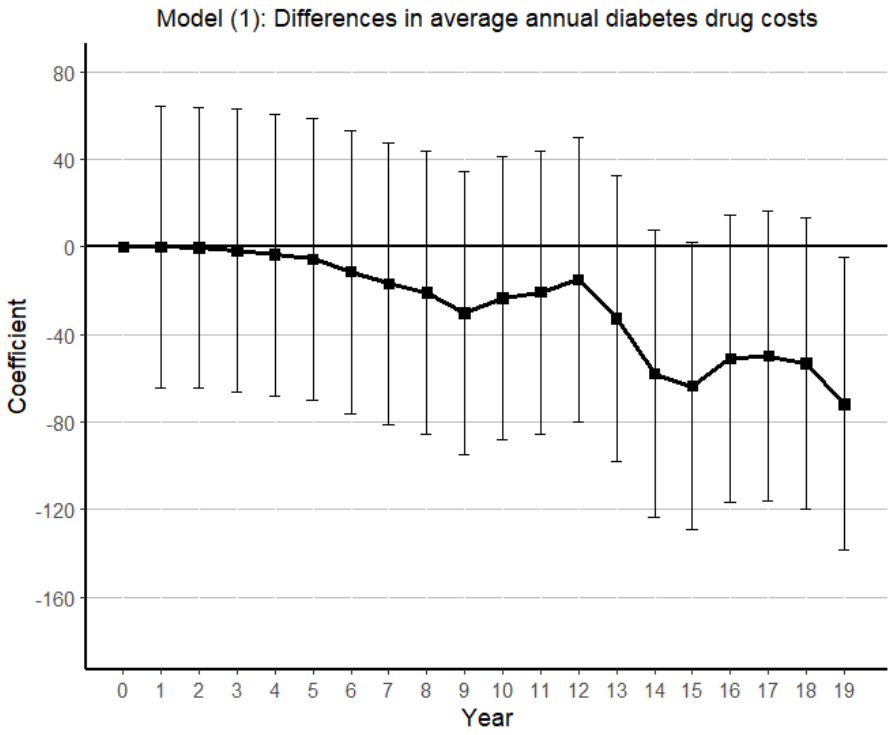

Figure 9: Differences in average annual diabetes drug costs

Table A.2. in Appendix 2 shows the coefficients for differences in average cumulative diabetes drug costs. To illustrate the cost developments, predicted cumulative average drug costs derived from the Model (2) are presented in Figure 10. Confidence intervals are displayed at the level of 95%. Each point represents average cumulative costs of participants involved in the calculation from year 1 to the year under examination, similarly as in Chapter 5.2. By the end of the follow-up period, cumulative diabetes drug costs were on average slightly over €2000 for the intervention group and €2700 for the control group. The estimates of Model (2) are statistically significant at the level of five percent for years 17, 18 and 19.

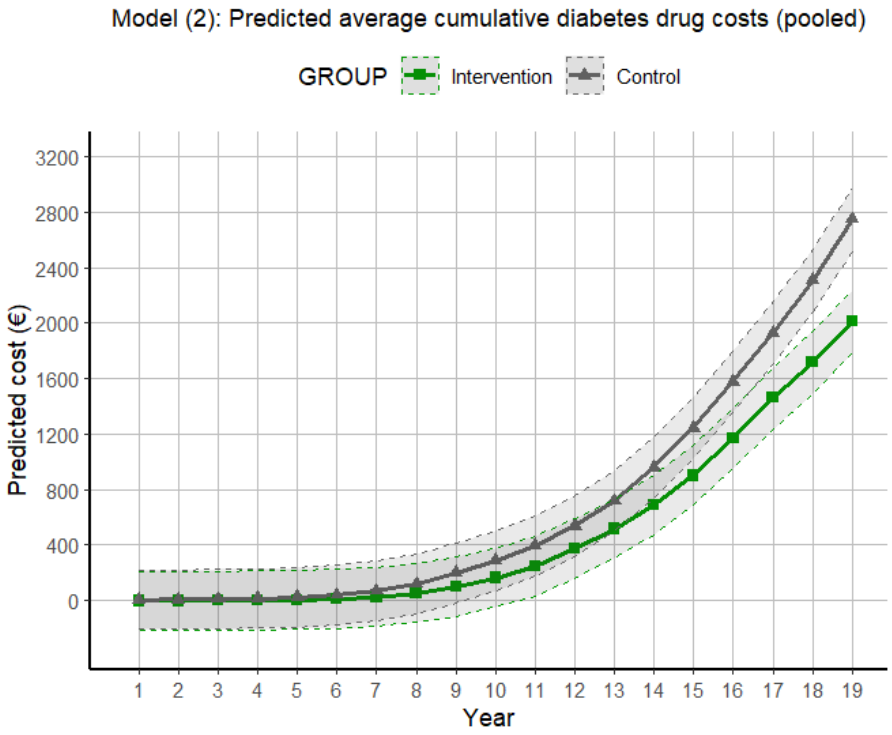

Figure 10: Predicted average cumulative diabetes drug costs (pooled)

Figure 11 displays the coefficients obtained from Model (1). The coefficients represent the annual differences in average cumulative costs, adjusted with two-way fixed effects. Confidence intervals of 95 % are presented in Figure 11. Again, the effects of similar size are found but slightly better statistical efficiency is gained by the Model (1). According to Table A.2., the differences are significant at the level of five percent for years 16, 17, 18 and 19. Over the 19-years follow up, the intervention group had on average €673 ($p<0.01$) lower cumulative diabetes drug costs, compared with the control group.

The results of the alternative two-part model are presented in Table A.8., in the Appendix 4. According to the logistic part of the model, individuals in the intervention group had, on average, 0.155 lower odds of having any diabetes costs over 19 years, compared with individuals in the control group. The negative coefficient indicates that individuals in the intervention group were less likely to accumulate any diabetes drug costs. However, the coefficient is not statistically significant. According to the second GLM-part, cumulative diabetes drug costs were on average nearly 22 % (exp(-0.246)-1) ($p>0.05$) lower in the intervention group over 19 years, compared with the control group, among those who had accumulated any costs. Neither this difference is statistically significant. However, the direction of these results is similar to those of Model (1).

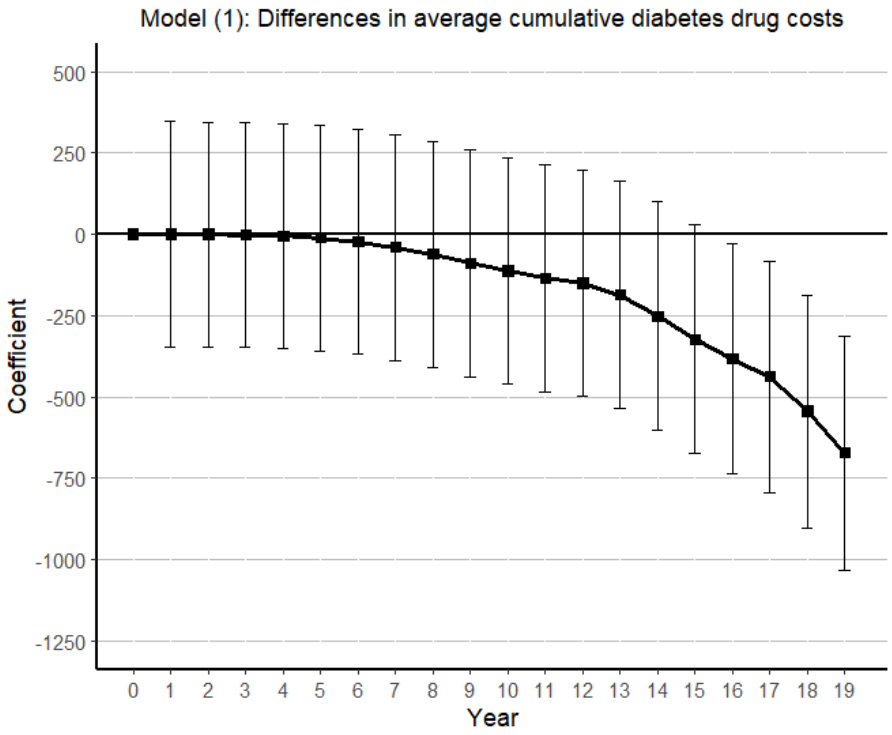

Figure 11: Differences in average cumulative diabetes drug costs

5.4 Cardiovascular drug costs

The impacts of the intervention on cardiovascular drug costs are studied in this subchapter. This analysis includes all drug purchases classified under the ATC code C. Table A.5. in Appendix 3 shows the regression coefficients for both Models (1) and (2), annual cardiovascular drug costs as the outcome. Each coefficient is the interaction between the intervention indicator LI and relative time. The interactions represent the effect of the intervention on cardiovascular drug costs at each point of relative time. To convert the costs into 2021 currency, the cost-of-living index (Consumer price index 2022) was used.

The predicted average developments for annual costs are displayed in Figure 12, which is based on the pooled Model (2). Confidence intervals are presented at the level of 95%. Based on Figure 12, the trends appear to be relatively similar over the first nine years. The average costs were at their highest in year 9, at which they were around €350 for both groups. Afterwards, the average costs of the intervention group remained at higher level compared with the control group. Interestingly, Figure 12 shows the U-shaped trends for both groups. This may be partly attributed to the general societal trend regarding cardiovascular drug costs. Since 2008 the trend in cardiovascular drug costs has been

declining (Kelasto 2023). At year 19, average cardiovascular drug costs were around €250 and €205 for the intervention and control groups. However, coefficients of the Model (2) are not statistically significant. This is intuitive especially for the first 14 years as the differences are relatively small.

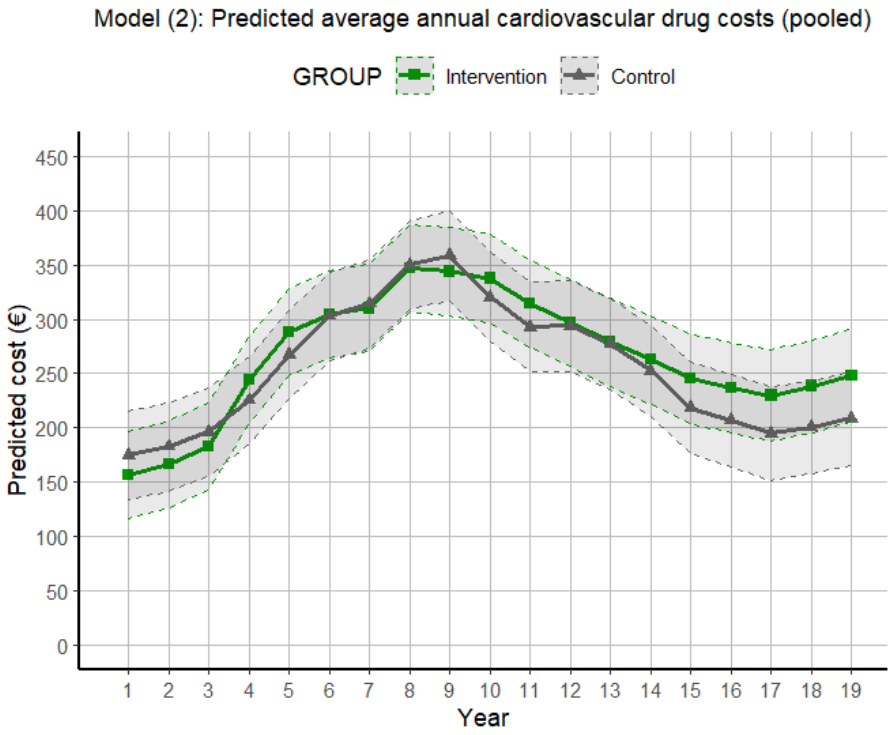

Figure 12: Predicted average annual cardiovascular drug costs (pooled)

Figure 13 shows the differences in annual average cardiovascular drug costs, based on the Model (1) with two-way fixed effects. Similarly, 95% confidence intervals are shown. The annual cardiovascular drug costs were on average €11 lower in the intervention group over the first three years, compared with the control group. Over the last ten years, the intervention group had, on average, €33 higher annual costs per participant. The difference was at its highest in year 19, at which the intervention group had €45 ($p>0.05$) higher average costs. Again, confidence intervals are wide indicating uncertainty in the results, and statistical significancy is not observed. However, these results are in line with DPS. According to Lindström et al. (2021), evidence of long-term impacts on the incidence of diabetes related diseases was limited during DPS.

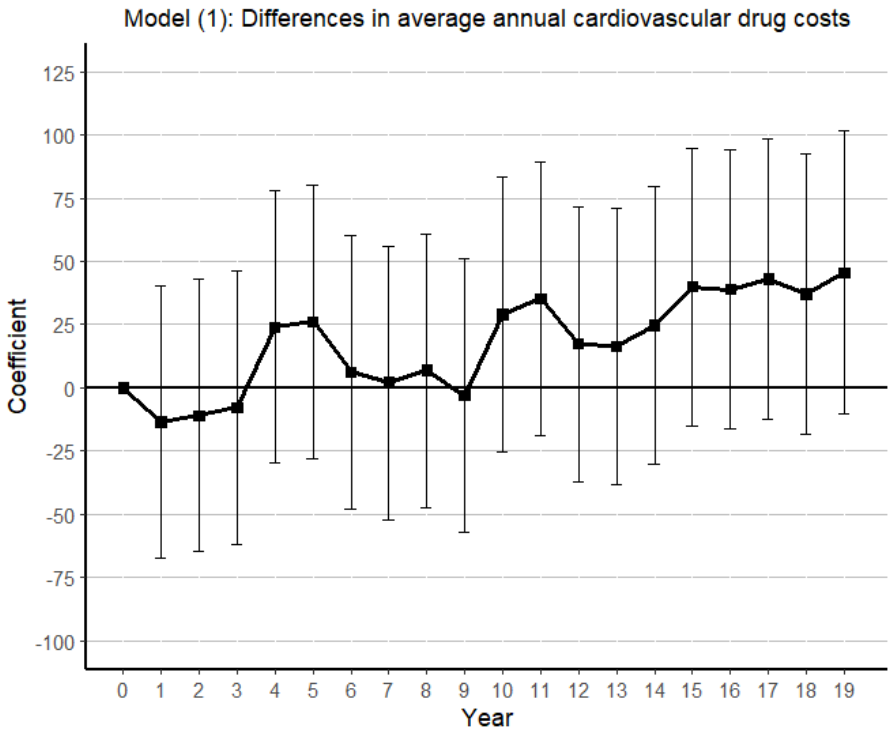

Figure 13: Differences in average annual cardiovascular drug costs

Average cumulative cardiovascular drug costs are examined in following figures. Regression coefficients for Models (1) and (2) are shown in Table A.6., in Appendix 3. Predicted average cumulative cardiovascular drug costs derived from Model (2) are presented in Figure 14. Confidence intervals of 95% are displayed in Figure 14. Similarly as earlier in Chapter 5, each point represents average cumulative costs of involved participants from year 1 to the year examined. According to the Figure 14, average cumulative costs were close to similar for the groups over the first 15 years. However, over the 19-year follow up, the intervention group had higher average cumulative costs compared with the control group. Cumulative cardiovascular drug costs were on average nearly €5000 and over €4600 for the intervention and control groups. The coefficients of Model (2) are not, however, statistically significant.

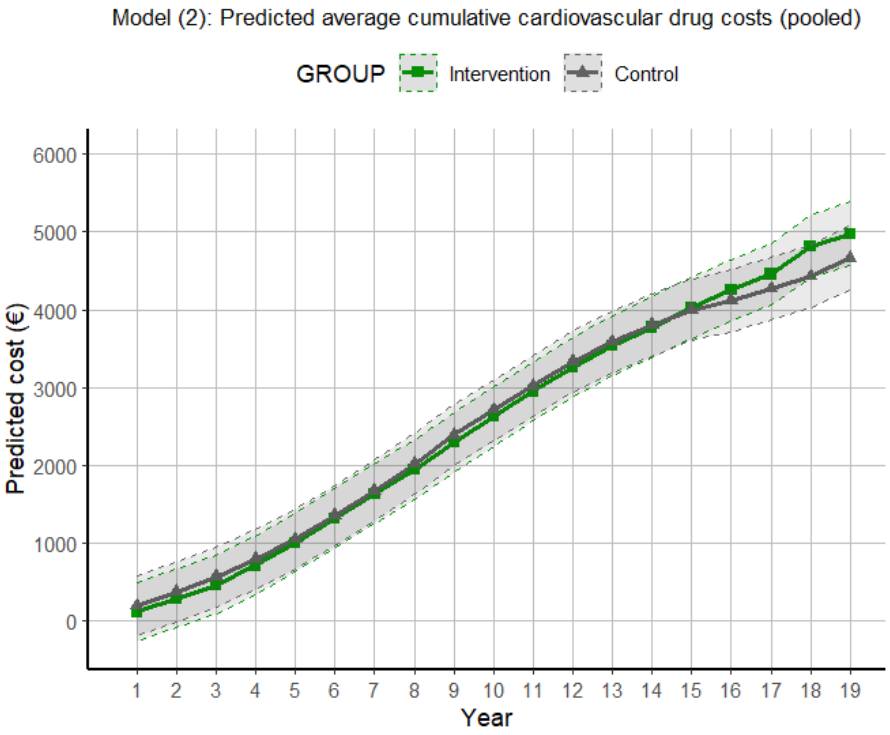

Figure 14: Predicted average cumulative cardiovascular drug costs (pooled)

Annual regression coefficients of Model (1) are displayed in Figure (15). They represent the annual differences in average cumulative cardiovascular drug costs, adjusted with individual and time fixed effects. Confidence intervals are shown at the level of 95%. Compared with the pooled Model (2), differences are obtained slightly earlier. The cumulative costs for the intervention group appear to be higher from year 10 the year 19, compared with the control group. According to the results of Model (1), the intervention group had on average €356 ($p>0.05$) higher cumulative cardiovascular drug costs compared with the control group. However, Table A.6 shows that the results lack of statistical significancy.

The alternative two-part model, the results of which are shown in in Table A.9., in Appendix 4, support these findings. In the logit-part, the positive coefficient of LI indicates higher average probability for the individuals in the intervention group to accumulate any cardiovascular drug costs over 19 years. The GLM-model in the second part estimates 7% higher average cumulative costs for the intervention group among those who have accumulated any costs over 19 years. These findings are not statistically significant. However, the results are similar to the results of Model (1).

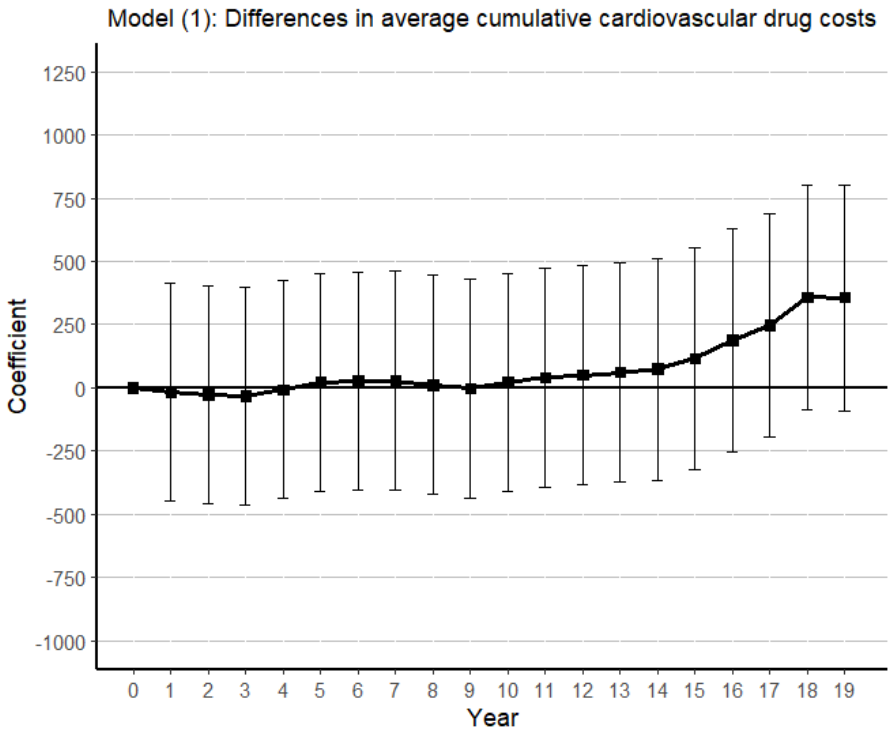

Figure 15: Differences in average cumulative cardiovascular drug costs

6 Discussion

The costs of diabetes have increased considerably in recent decades. As I demonstrated in Chapter 3, the growth in diabetes drug costs is associated at least with the substantial increase in the number of diabetics, as well as the introduction of new and more expensive drugs. In Finland, acts to reduce the societal burden caused by diabetes have included for instance implementations of several cost-saving reforms and modifications of the reimbursement system. For instance, in 2016 the reimbursement rate of antidiabetic drugs other than insulins was lowered from 100 to 65 percent (Government proposal 184/2016).

According to Jarvala et al. (2010; 17, 27), total drug costs, including all drug purchases, were around 25% of the total healthcare costs for diabetics in Finland in 2007, meaning €1100 per diabetic individual[21]. In 2021, the costs of diabetes drugs (A10) were €611 per individual with diabetes (Kelasto 2023). These numbers are not directly comparable to those presented in this thesis, since according to Lindström et al. (2013), only around half of the DPS-participants were diagnosed with diabetes during 16-years period. In addition, the diagnoses were relatively recent, and therefore suffering from diabetes related complications may have been lower than among average diabetics. This in turn may have reduced drug consumption.

For instance, Li et al. (2013, 1) estimated that the mean annual direct medical cost for a man with recent diabetes diagnosis without complications or comorbidities is around $2500. Assuming that the share used for drugs is approximately the same calculated by Jarvala et al. (2010), the mean annual drug cost would be around $625. Obviously, this approximation is not entirely comparable due to, for instance, different time periods, healthcare systems and target populations. In addition, I did not observe the exact moments of diagnoses which is why comparison with approximations like the one by Li et al. (2013, 1) is difficult. However, a rough comparison shows that the cost trends observed in this thesis are quite intuitive, especially in late years of the follow up period.

The results of this thesis, regarding diabetes drug costs, are as expected. Compared with the control group, the incidence of diabetes has been observed to remain lower in the intervention group at least for 13 years (Lindström et al. 2013). Hence, it is intuitive that

[21] This is approximately €1335 in terms of 2021 currency, based on the Cost-of-living index provided by Statistics Finland.

the costs of diabetes drugs were estimated to be lower in the intervention group. The differences in average annual costs were the largest over the last seven years of the follow-up, over which the intervention group had on average €54 lower annual diabetes drug costs. However, only the difference of year 19 was statistically significant. Instead, the average cumulative costs were observed to be €673 ($p<0.01$) lower in the intervention group over 19 years.

However, the differences observed in total drug costs are instead surprising, knowing that Type 2 diabetes is related to many other diseases. Regardless of the slightly lower annual average costs in the intervention group over the first three years ($p>0.05$), the costs appeared to remain at higher level in the longer term, compared with the control group ($p>0.05$). The average cumulative total drug costs were €736 ($p>0.05$) higher in the intervention group over 19 years. This is at least partly attributed to costs for cardiovascular drugs. The cumulative costs of cardiovascular drugs were on average €356 ($p>0.05$) higher for the intervention group than for the control group. In addition, cumulative costs in some other drug classes not observed in this thesis might have been, on average, slightly higher for the intervention group. However, these results are in line with earlier results from DPS since the effects of the intervention on diabetes related diseases have not been found (Lindström et al. 2021).

In Chapter 5.2 I noted that diabetes diagnosis is an information shock. By affecting health behaviour, it can impact on the measured effectiveness of an intervention. According to Gaggero et al. (2022), weight reduction is greater at least three years after the diabetes diagnosis. Since the control group received more diagnoses during the DPS (Lindström 2003, 3234), it was also exposed to a higher number of these information shocks. This might partly bias the results if these shocks have affected positively the average health of the control group. If so, improved health may have had negative effect on average drug costs for the control group.

The correct use of medication has been found to lower health care use and costs by reducing for instance hospitalization and emergency department use (Stuart et al. 2009; Roebuck et al. 2011). Moreover, it has been found to reduce indirect costs such as employee absenteeism (Rizzo et al. 1996) and even prevent Type 2 diabetes (The Diabetes Prevention Program Research Group 2003; 2009). Hence, higher drug costs do not necessarily imply for higher overall health care costs. Higher drug costs of the

intervention group might have been due to frequent health care visits and lifestyle advice, and hence, improved knowledge of correct use of drugs. Moreover, these frequent visits during the intervention may have lowered participants' threshold to seek medical attention when required in the later years. In any case, these factors might have led to, for instance, better adherence to prescription drugs, which increases overall costs but can reduce the use of expensive health care services in the future.

Moreover, the intervention may have had wider spillover effects on spouses or others living in the same household, as they may also have benefited from the lifestyle advice (see e.g., Basu & Melzer 2005; Angelucci & Di Maro 2016). For example, family members may have followed the same diet and therefore improved their lifestyles. This may have reduced, for example, the use of health care services by family members of the intervention group. A method to account for these spillovers, and other direct and indirect costs, would be necessary in order to determine the cost-effectiveness of the intervention.

Interpretations about the cost-effectiveness of DPS cannot be made based on my thesis since indirect or direct costs other than drug costs were not observed. As reviewed in Chapter 4, however, results from other studies have shown promising findings regarding the cost-effectiveness of diabetes prevention. However, these results are usually sensitive to, for instance, the methods and measures used, and the duration of the study period. In addition, simulating the effects of nationwide intervention is challenging, as several crucial factors such as participation rate, patients' selection, and adherence, as well as the context and the target population might differ significantly in real-world implementation compared to a controlled trial. Therefore, even if all possible direct and indirect costs of the DPS were observed, the results would not necessarily be directly useable for a decision maker. Cost-effective ratio of the intervention could significantly change if the intervention was implemented in Finnish primary health care.

Drawing conclusions is also challenging due to the fact that only few of the findings were statistically significant at the level of five percent. This could be due to at least three reasons. First, variances in costs were large in all classes and appeared to increase over time. This resulted particularly in wide confidence intervals, which indicate uncertainty in the estimates. Second, the data might not be large enough to observe statistically significant results as the differences are this small, especially when the variances are

large[22]. Third, high p-values might, in general, appear when there are no differences in the impacts of an intervention or when the impacts are relatively small. In the context of this thesis, the sample size of slightly over 500 participants complicates statistical inferences, as variances are this large. Simply, there is not enough "mass" to prove that the differences observed are not a coincidence. On the other hand, none of the differences were either remarkably large. However, it might be that significant savings in overall drug costs cannot be expected with an intervention like DPS.

This thesis is the first to present the impacts of the DPS intervention on drug costs. In this thesis, an exceptionally long follow-up period was observed. It is usual that RCT-based studies consider only short period of time. In addition, dropout rate among the participants was relatively low, which improves the reliability of the results. Higher dropout rate could be an issue in situations where only certain types of individuals dropped out. This could violate the initial randomization. On the other hand, over 14 % of the participants died during the 19-year follow-up, which might hinder especially the interpretation of the late years results. Within diabetes drugs, however, average costs were lower for the intervention group over the whole follow-up period, which also supports the longer-term results.

The reimbursement rate of antidiabetic drugs was lowered from 100 % to 65 % in 2017 (HE 184/2016). However, previous studies have found that copayment correlates negatively with adherence to diabetes medication (Chernew et al. 2008; Barron et al. 2008; Colombi et al. 2008; Hunt et al. 2009). Since this poor adherence may result to increased health care and labour market costs (Stuart et al. 2009; Rizzo et al. 1996), the net savings of the 2017 reform might be less than €150 million which was the aim set by the Finnish government. In addition, the government assessed that the reform would affect low-income patients the most (HE 184/2016), which also raises the issue of equity.

Indeed, even though cutting the reimbursement rate may temporarily reduce reimbursement expenses, it does not necessarily slow down the continuous increase in the burden of the disease in the society. Hence, it would be worth to consider whether the preventative intervention like the DPS could lead to equal savings in reimbursement

[22] In some cases, on the other hand, when a sample size is large, even small differences might appear as statistically significant, causing potentially misleading interpretations of the results (McCloskey & Ziliak, 2008).

expenses for diabetes drugs, or cost-effective health improvements, in the longer term. The impacts of a successful lifestyle intervention might not necessarily appear as reduced total drug costs but instead as reduced use of health care services or improved labour market outcomes. The intervention could, in addition to economic effects, have positive impacts on public health and equity. However, additional research is still needed especially regarding the cost-effectiveness of diabetes prevention interventions in public health care.

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Appendices

Appendix 1 Regression tables for total drug costs

Table A. 1: Differences in annual average total drug costs

Differences in annual average total drug costs

	Dependent variable:	
	Annual total drug costs	
	Model (1)	Model (2)
LI * time(1)	13.659 (81.351)	15.049 (109.691)
LI * time(2)	-11.796 (81.348)	-11.165 (109.691)
LI * time(3)	-35.005 (81.503)	-37.315 (109.850)
LI * time(4)	13.485 (81.503)	11.175 (109.850)
LI * time(5)	31.407 (81.604)	37.468 (109.963)
LI * time(6)	-23.770 (81.604)	-17.960 (109.963)
LI * time(7)	14.427 (81.698)	15.164 (110.074)
LI * time(8)	-13.666 (81.744)	-26.504 (110.129)
LI * time(9)	-4.179 (81.887)	4.569 (110.303)
LI * time(10)	60.855 (81.887)	69.570 (110.303)
LI * time(11)	51.123 (81.983)	60.400 (110.422)
LI * time(12)	59.901 (82.172)	73.464 (110.658)
LI * time(13)	36.809 (82.407)	42.129 (110.954)
LI * time(14)	52.331 (82.831)	50.143 (111.489)
LI * time(15)	142.728* (82.981)	144.062 (111.676)
LI * time(16)	81.616 (83.175)	100.325 (111.923)
LI * time(17)	97.162 (83.613)	103.730 (112.483)
LI * time(18)	35.451 (84.167)	56.017 (113.189)
LI * time(19)	-99.127 (84.608)	-86.439 (113.732)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.011	0.112
Adjusted R^2	-0.050	0.108
F Statistic	2.864*** (df = 37; 9155)	28.312*** (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Table A. 2: Differences in average cumulative total drug costs

Differences in average cumulative total drug costs

	Dependent variable:	
	Cumulative total drug costs	
	Model (1)	Model (2)
LI * time(1)	5.632 (507.379)	15.049 (799.048)
LI * time(2)	-2.953 (507.361)	3.884 (799.048)
LI * time(3)	-39.954 (508.327)	-55.937 (800.207)
LI * time(4)	-26.551 (508.332)	-42.662 (800.207)
LI * time(5)	36.652 (508.958)	42.204 (801.032)
LI * time(6)	20.052 (508.957)	25.029 (801.032)
LI * time(7)	18.599 (509.547)	3.112 (801.840)
LI * time(8)	-72.654 (509.830)	-130.662 (802.234)
LI * time(9)	45.567 (510.727)	75.125 (803.505)
LI * time(10)	119.003 (510.727)	147.997 (803.505)
LI * time(11)	199.807 (511.323)	217.032 (804.369)
LI * time(12)	334.478 (512.500)	350.771 (806.092)
LI * time(13)	301.649 (513.969)	312.064 (808.246)
LI * time(14)	291.877 (516.614)	277.713 (812.141)
LI * time(15)	451.080 (517.547)	462.853 (813.505)
LI * time(16)	718.308 (518.755)	865.265 (815.309)
LI * time(17)	735.472 (521.489)	804.809 (819.386)
LI * time(18)	886.819* (524.947)	1,088.471 (824.526)
LI * time(19)	735.508 (527.697)	872.771 (828.484)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.002	0.331
Adjusted R^2	-0.060	0.328
F Statistic	0.380 (df = 37; 9155)	111.562*** (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Appendix 2 Regression tables for diabetes drug costs

Table A. 3: Differences in annual average diabetes drug costs

Differences in annual average diabetes drug costs

	Dependent variable:	
	Annual diabetes drug costs	
	Model (1)	Model (2)
LI * time(1)	0.013 (32.805)	-0.136 (40.770)
LI * time(2)	-0.447 (32.803)	-0.635 (40.770)
LI * time(3)	-1.715 (32.866)	-1.462 (40.829)
LI * time(4)	-3.643 (32.866)	-3.389 (40.829)
LI * time(5)	-5.608 (32.907)	-4.976 (40.871)
LI * time(6)	-11.528 (32.907)	-10.896 (40.871)
LI * time(7)	-16.904 (32.945)	-16.246 (40.912)
LI * time(8)	-20.922 (32.963)	-20.311 (40.932)
LI * time(9)	-30.263 (33.021)	-30.405 (40.997)
LI * time(10)	-23.560 (33.021)	-23.852 (40.997)
LI * time(11)	-20.854 (33.060)	-21.454 (41.041)
LI * time(12)	-14.950 (33.136)	-15.230 (41.129)
LI * time(13)	-32.767 (33.231)	-34.166 (41.239)
LI * time(14)	-58.068* (33.402)	-60.049 (41.438)
LI * time(15)	-63.688* (33.462)	-65.881 (41.507)
LI * time(16)	-51.062 (33.540)	-53.862 (41.600)
LI * time(17)	-49.914 (33.717)	-53.866 (41.808)
LI * time(18)	-53.417 (33.940)	-61.036 (42.070)
LI * time(19)	-71.946** (34.118)	-82.826* (42.272)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.004	0.163
Adjusted R^2	-0.057	0.159
F Statistic	1.015 (df = 37; 9155)	43.677*** (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Table A. 4: Differences in average cumulative diabetes drug costs

Differences in average cumulative diabetes drug costs

	Dependent variable:	
	Cumulative diabetes drug costs	
	Model (1)	Model (2)
LI * time(1)	0.560 (176.379)	-0.136 (216.489)
LI * time(2)	-0.096 (176.373)	-0.771 (216.489)
LI * time(3)	-1.993 (176.709)	-1.318 (216.803)
LI * time(4)	-5.791 (176.711)	-5.087 (216.803)
LI * time(5)	-11.137 (176.928)	-8.712 (217.026)
LI * time(6)	-22.731 (176.928)	-20.294 (217.026)
LI * time(7)	-39.754 (177.133)	-37.175 (217.245)
LI * time(8)	-60.667 (177.231)	-58.530 (217.352)
LI * time(9)	-89.323 (177.543)	-91.342 (217.696)
LI * time(10)	-112.765 (177.543)	-114.908 (217.696)
LI * time(11)	-135.490 (177.750)	-139.090 (217.930)
LI * time(12)	-150.364 (178.159)	-153.541 (218.397)
LI * time(13)	-185.907 (178.670)	-193.588 (218.980)
LI * time(14)	-252.235 (179.589)	-263.692 (220.036)
LI * time(15)	-322.931* (179.914)	-333.725 (220.405)
LI * time(16)	-383.741** (180.334)	-397.229* (220.894)
LI * time(17)	-438.214** (181.284)	-459.850** (221.999)
LI * time(18)	-544.242*** (182.486)	-581.246*** (223.391)
LI * time(19)	-672.536*** (183.442)	-722.181*** (224.464)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.010	0.174
Adjusted R^2	-0.051	0.170
F Statistic	2.509*** (df = 37; 9155)	47.309*** (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Appendix 3 Regression tables for cardiovascular drug costs

Table A. 5: Differences in annual average cardiovascular drug costs

Differences in annual average cardiovascular drug costs

	Dependent variable:	
	Annual cardiovascular drug costs	
	Model (1)	Model (2)
LI * time(1)	-13.450 (27.458)	-12.816 (41.186)
LI * time(2)	-11.060 (27.457)	-10.944 (41.186)
LI * time(3)	-7.852 (27.509)	-7.962 (41.246)
LI * time(4)	24.048 (27.510)	24.072 (41.246)
LI * time(5)	26.087 (27.543)	26.680 (41.289)
LI * time(6)	6.168 (27.543)	6.669 (41.289)
LI * time(7)	2.036 (27.575)	1.500 (41.330)
LI * time(8)	6.906 (27.591)	2.090 (41.351)
LI * time(9)	-3.088 (27.639)	-9.222 (41.416)
LI * time(10)	29.075 (27.639)	22.655 (41.416)
LI * time(11)	35.294 (27.671)	27.038 (41.461)
LI * time(12)	17.363 (27.735)	8.322 (41.549)
LI * time(13)	16.463 (27.815)	7.312 (41.660)
LI * time(14)	24.623 (27.958)	15.432 (41.861)
LI * time(15)	39.915 (28.008)	32.199 (41.931)
LI * time(16)	38.874 (28.074)	35.406 (42.024)
LI * time(17)	43.041 (28.222)	40.166 (42.235)
LI * time(18)	37.084 (28.409)	43.509 (42.499)
LI * time(19)	45.463 (28.557)	44.711 (42.704)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.013	0.089
Adjusted R^2	-0.048	0.085
F Statistic	3.272^{***} (df = 37; 9155)	22.020^{***} (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Table A. 6: Differences in average cumulative cardiovascular drug costs

Differences in average cumulative cardiovascular drug costs

	Dependent variable:	
	Cumulative cardiovascular drug costs	
	Model (1)	Model (2)
LI * time(1)	-18.876 (219.555)	-12.816 (389.409)
LI * time(2)	-27.867 (219.547)	-23.760 (389.409)
LI * time(3)	-32.759 (219.965)	-41.835 (389.974)
LI * time(4)	-7.717 (219.967)	-16.616 (389.974)
LI * time(5)	20.121 (220.238)	17.090 (390.376)
LI * time(6)	27.881 (220.238)	24.521 (390.376)
LI * time(7)	27.566 (220.493)	19.225 (390.770)
LI * time(8)	11.134 (220.615)	-14.602 (390.962)
LI * time(9)	-3.171 (221.004)	-36.970 (391.581)
LI * time(10)	20.925 (221.004)	-13.089 (391.581)
LI * time(11)	39.963 (221.261)	-7.182 (392.002)
LI * time(12)	49.678 (221.771)	-6.847 (392.841)
LI * time(13)	61.340 (222.407)	10.794 (393.891)
LI * time(14)	74.035 (223.551)	29.894 (395.790)
LI * time(15)	116.894 (223.955)	85.091 (396.455)
LI * time(16)	188.201 (224.477)	194.557 (397.334)
LI * time(17)	246.585 (225.660)	249.357 (399.320)
LI * time(18)	357.474 (227.157)	453.774 (401.825)
LI * time(19)	355.752 (228.347)	370.812 (403.754)
Twoway FE	X	
Baseline controls		X
Observations	9,721	9,721
R^2	0.002	0.238
Adjusted R^2	-0.060	0.234
F Statistic	0.421 (df = 37; 9155)	70.201^{***} (df = 43; 9677)
Note:		*p<0.1; **p<0.05; ***p<0.01

Appendix 4 Regression tables for alternative two-part models

Table A. 7: Average cumulative total drug costs (19 years)

GLM-model: Average cumulative total drug costs (19 years)

	Dependent variable:
	Log(Cumu_total)
LI	0.072 (0.079)
Constant	9.466*** (0.056)
Observations	439
Log Likelihood	-4,594.666
Akaike Inf. Crit.	9,193.331
Note:	*p<0.1; **p<0.05; ***p<0.01

Table A. 8: Average cumulative diabetes drug costs (19 years)

Two-part model: Average cumulative diabetes drug costs (19 years)

	Dependent variable:	
	Cumu_diab *logistic*	Cumu_diab *glm: Gamma link = log*
	(1)	(2)
LI	-0.155 (0.198)	-0.246 (0.157)
Constant	0.625*** (0.142)	8.345*** (0.110)
Observations	439	278
Log Likelihood	-288.204	-2,543.518
Akaike Inf. Crit.	580.409	5,091.036
Note:		*p<0.1; **p<0.05; ***p<0.01

Table A. 9: Average cumulative cardiovascular drug costs (19 years)

Two-part model: Average cumulative cardiovascular drug costs (19 years)

	Dependent variable:	
	Cumu_cardiov	Cumu_cardiov
	logistic	*glm: Gamma link = log*
	(1)	(2)
LI	0.237 (0.386)	0.068 (0.095)
Constant	2.536*** (0.260)	8.506*** (0.067)
Observations	439	410
Log Likelihood	-106.630	-3,901.986
Akaike Inf. Crit.	217.260	7,807.972
Note:		*p<0.1; **p<0.05; ***p<0.01