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Growth of diabetes drug expenditure decomposed—A nationwide analysis

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ABSTRACT

Objectives: The aim of this study was to quantify different factors underlying the growth of diabetes drug expenditure in Finland.
Methods: Data representing purchases of antidiabetic agents between 2003 and 2015 were extracted from a nationwide prescription register. By using Fisher's Ideal Indexes, the per capita expenditure growth for both insulins and non-insulin antidiabetic agents was decomposed into six different determinants: purchase volume, purchase size, switches between therapeutic classes, switches within therapeutic classes, unit costs and switches to generic alternatives.
Results: Between 2003 and 2015, the per capita expenditure on insulins increased by €8.64 and on non-insulins by €13.73. For insulins, holding other factors constant, change in the number of purchases represented a €4.67 increase in expenditure, change in the size of purchases a €4.33 increase and switches between therapeutic classes a €4.07 increase. For non-insulins, change in the number of purchases represented a €10.22 increase in expenditure and switches between therapeutic classes, a €10.17 increase. Changes in purchase size increased the non-insulin per capita expenditure by €1.48. For both insulins and non-insulins, changes in prices and product level switches had decreasing effects on expenditures.
Conclusions: The main drivers of the growth in diabetes drug expenditure were volume growth and switches to newer and more expensive drugs. Price changes, however, had a decreasing effect on the overall diabetes drug expenditure.

1. Introduction

The use of antidiabetic agents has almost doubled in the member countries of the Organization for Economic Co-Operation and Development (OECD) during the 2000s because of the rising prevalence of diabetes [1]. In Europe, the number of diabetes patients is estimated to increase from 60 million to 71 million by 2040 [2].

Finland ranks close to the EU and OECD averages in diabetes prevalence (6% vs. 6% vs. 8%) but has the highest consumption of antidiabetic agents among OECD countries (86 vs. 62 defined daily doses (DDDs)/1000 inhabitants/day in Finland vs. OECD average) [1,3]. Antidiabetic agents constitute one of the biggest therapeutic groups contributing to the total expenditure on reimbursed drugs in Finland. Between 2003 and 2015, the share of antidiabetic agents of the total expenditure increased from 8% to 15% [4,5]. In 2015, the top ten list of drugs with the highest total sales value contained three diabetes drugs, and three out of the top five drugs with the highest reimbursement costs were for treating diabetes [6,7]. The growth in diabetes drug expenditure has been notably steeper than the increase in the number of diabetes drug users.

During the past two decades, a wide variety of new diabetes drugs has been introduced worldwide. In Finland, their uptake has been particularly rapid, at least in comparison to other Nordic countries. In 2015, the share of DPP-4 inhibitors of all non-insulin consumption and the share of long-acting insulin of all insulin consumption was approximately two to three times higher in Finland than it was in Sweden, Norway and Denmark [8–10]. New drugs tend to be more expensive than existing ones, and thus insurance and reimbursement policies play a major role in their uptake. In Finland, long-acting insulin analogues overtook NHP-insulins as the most preferred insulin option within 2 years after inclusion to the higher reimbursement category (2003 for type 1 diabetes

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and 2007 for type 2 diabetes) [11]. As for non-insulin antidiabetic agents, sulfonylureas were replaced by dipeptidyl peptidase 4 (DPP-4) inhibitors as the most used second line option in 2011, one year after the first DPP-4 inhibitor received the higher reimbursement status. More recently, the use of glucagon-like peptide-1 (GLP-1) analogues has seen a particularly rapid increase [11].

Controlling the growth of pharmaceutical expenditures so that the allocation of resources on drug therapy is cost effective has been one of the most important issues in pharmaceutical policy since the 1980s and 1990s. At the same time, decision makers balance between other, partly competing pharmaceutical policy goals: guaranteeing equal access to necessary treatments, ensuring the quality and safety of treatments and promoting innovation [12–14]. Moreover, expenditure growth is simultaneously affected by more than one factor, and the different factors may have opposing or overlapping impacts. Controlling expenditures wisely thus requires understanding the dynamics behind the growth trends and targeting policy measures accordingly.

In general, factors that contribute to increases in drug expenditure can be categorized as volume effects, price effects and therapeutic choices [15]. In previous studies, where the drug expenditure growth is decomposed into the aforementioned categories, increase in volume and changes in prescribing patterns towards newer and more expensive products have been identified as the main determinants of drug expenditure growth. However, the results vary between countries with different regulatory settings as well as between different therapeutic classes and time periods within countries [16–22].

Given the significant role of diabetes drugs in total drug expenditure in Finland, the aim of this study is to decompose and quantify the increase in Finnish diabetes drug expenditure between 2003 and 2015.

2. Materials and methods

2.1. Settings

The prescription pharmaceutical market in Finland is highly regulated. The reimbursement status and the wholesale price of a drug product in an outpatient setting are evaluated and approved by the Pharmaceuticals Pricing Board, operating under the Ministry of Social Affairs and Health [23]. The retail price of a reimbursable prescription drug consists of the approved wholesale price, regulated pharmacy margin and value added tax (10%) and thus the price of the product is the same in all Finnish pharmacies. All permanent Finnish residents are eligible for reimbursed drugs under the National Health Insurance (NHI). In 2015, reimbursed drugs accounted for 94% of the total costs for outpatient prescription drugs [24]. The rate of reimbursement depends on disease severity. During our study period, diabetes was one of the diseases that warrant the highest rate of reimbursement, 100% with a €3 fixed prescription fee per prescription item for up to three months' supply. However, at the time of the study, two years' experience of use after approval for reimbursement at the basic rate (35% in 2015) was generally needed before a product could be included in higher reimbursement categories [25].

Finland, like many other countries, has introduced several market reforms to contain drug costs and intensify price competition. After patent expiry, products are subject to generic substitution (since 2003) and generic reference pricing (since 2009) [26,27]. However, within antidiabetic agents, only oral formulations are substitutable at pharmacy level. As statutory savings measures, the wholesale prices of reimbursed products were cut by 5% in 2006 and again in 2013, although in the latter case products subject to generic substitution and reference pricing were exempt [28,29]. The reduction in 2013 influenced especially the pricing of the newest antidiabetic drugs not included in generic substitution.

2.2. Data

The data for this study was obtained from the nationwide Prescription Register, which is maintained by The Social Insurance Institution of Finland (Kela), and contains records of all purchases of reimbursed prescription drugs in outpatient care. For this study, all records of purchases of products in the ATC class A10 (drugs used in diabetes) between 1 January 2003 and 31 December 2015 were extracted from the register. ATC refers to the Anatomical Therapeutic Chemicals classification of the WHO Collaborating Center for Drug Statistics Methodology [30]. For each purchase, information on the dispensing date, ATC code, product identification code (Nordic article number, VNR), total cost of the purchase and number of defined daily doses (DDDs) [30], were retrieved. A DDD has not been assigned for guar gum (ATC class A10BX01) and therefore guar gum purchases were excluded from all analyses. In 2003–2015, purchases of products containing guar cum accounted for 0.6–0.03% of total costs of drugs within ATC class A10. Finally, we standardized all cost data to 2015 euros using the Consumer Price Index.

The costs used in the analyses are total retail costs of a purchase, including the NHI reimbursement, patient co-payment, and value added tax (VAT). We used cost per DDD as the unit cost. In the analysis, all expenditures are treated as costs per capita, instead of cost per user, to remove the effect of population growth. The DDDs for combination products, however, deviate from the DDDs assigned for plain preparations, which limit their comparability. Therefore, in our analyses, purchases of combination products were treated as if the active ingredients had been purchased separately. We classified purchases of combination products with multiple active ingredients into respective ATC classes based on the individual active ingredients, and their costs were allocated entirely to the ATC classes with higher unit costs. For example, the cost of a product containing both metformin and sitagliptin is allocated entirely to sitagliptin. Combination products were re-classified to capture the cost impact of changes from older to newer active ingredients rather than the cost impact of changes between formulations. However, to investigate how this re-classification might affect the results, we conducted a sensitivity analysis for non-insulins, where combination products were treated as separate groups of products according to their original ATC codes.

2.3. Methods

To assess different factors explaining the increase in per capita expenditure on diabetes drugs between 2003 and 2015, we use the Fisher Ideal Index decomposition method [20–22]. As previously published by Morgan [21], we decomposed the change in per capita expenditure into volume effects, therapeutic choices and price effects, each of which consists of two determinants further described in the paragraphs below. These determinants allowed us to investigate the simultaneous and opposing factors that have contributed to the changes in diabetes drug expenditure. Furthermore, the Fisher Index decomposition was chosen since it ensures consistency between the determinants and expenditure so that the product of the six determinants or three upper level categories will exactly equal the change in expenditure per capita during the study period (Eq. (1)) [31,32].

$$\Delta Expenditure\ per\ capita = \Delta Volume\ effects \times \Delta Therapeutic\ choices \times \Delta Price\ effects \quad (1)$$

Morgan [21] examined the different dynamics of drug spending by using therapeutic classes aggregated according to primary indication. The decomposition used in the present study is con-

structed on a more detailed level by using the different levels of the ATC classification system: pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4) and active ingredient (ATC level 5) [30]. Furthermore, we used a package-specific Nordic VNR number (package level), to capture changes at the product level (brand, formulation, package size, strength). The structure of the ATC system allows us to conduct separate decomposition analyses for the two pharmacological subgroups within diabetes drugs: insulins (ATC class A10 A) and non-insulin antidiabetic agents (ATC class A10B). Analysis conducted at this level gives a more precise description of the cost dynamics of diabetes drug expenditure compared to a decomposition for diabetes drugs as a single group.

Morgan [21] used dispensed units in measuring volume and limited the analyses to oral formulations to ensure consistency. In our analyses, to include all formulations (including injectables), we used defined daily doses instead of units. Compared to units, DDDs have the advantage of capturing changes in both strength and quantity of dispensed drugs. To include new products entering the market and older products exiting the market in the analyses without affecting the average costs, we projected the observed entry cost was projected backward to 2003 and the exit cost forward to 2015. For example, DPP-4 inhibitors entered the Finnish pharmaceutical market in 2007. To make the cost series complete for DPP-4 inhibitors, we took the observed entry price in 2007 and used it as a pre-entry price for the years 2003–2006. Similarly, we treated exiting products by taking the last observed price and used it as a post-exit price for the rest of the study period. This extension of the cost series is necessary because the weight terms of the Fisher Index require that all products have complete cost data during the entire study period.

2.4. Volume effects

Morgan [21] described volume effects as including "the volume of prescriptions dispensed and the size of those prescriptions". Both determinants are needed, since trends in purchase size may have an effect on purchase volume. For example, a larger quantity and/or stronger formulation of the drug per purchase could reduce the number of purchases. In our analyses, changes in purchase volume, i.e., changes in the number of purchases were captured by constructing a quantity index with expenditure data aggregated at pharmacological subgroup level (ATC level 3) (Eq. (2)). The effects of changes in purchase size were measured as the expenditure weighted average of changes in the number of DDDs (U) per purchase (P) at active ingredient level (ATC level 5) (Eq. (3)).

$$\Delta Purchase\ volume = \sqrt{\frac{\sum C^0_{atc3P} Q^t_{atc3P}}{\sum C^0_{atc3P} Q^0_{atc3P}} \times \frac{\sum C^t_{atc3P} Q^t_{atc3P}}{\sum C^t_{atc3P} Q^0_{atc3P}}} \quad (2)$$

$$\Delta Purchase\ size = \frac{\sqrt{\frac{\sum C^t_{atc5P} Q^0_{atc5P}}{\sum C^0_{atc5P} Q^0_{atc5P}} \times \frac{\sum C^t_{atc5P} Q^t_{atc5P}}{\sum C^0_{atc5P} Q^t_{atc5P}}}}{\sqrt{\frac{\sum C^t_{atc5U} Q^0_{atc5U}}{\sum C^0_{atc5U} Q^0_{atc5U}} \times \frac{\sum C^t_{atc5U} Q^t_{atc5U}}{\sum C^0_{atc5U} Q^t_{atc5U}}}} \quad (3)$$

where C_{atc3P} and Q_{atc3P} are aggregate expenditure and number of purchases of insulins and non-insulins (ATC level 3). C_{atc5P} and Q_{atc5P} are expenditure per purchase and number of purchases at ATC level 5. Similarly, C_{atc5U} and Q_{atc5U} are expenditure per DDD and number of DDDs. In the data, there are 16 observations for insulins and 18 observations for non−insulins at ATC level 5 (see tables 7 and 8 in the appendix). The superscript t represents current period and 0 base period.

2.5. Therapeutic choices

Under "therapeutic choices", Morgan [21] classified the influence of changes between alternative drug treatments and within therapeutic subgroups, i.e. into *therapeutic mix* and *drug mix*. In our analysis, the therapeutic mix measure captures the changes in expenditures at the pharmacological subgroup level (ATC level 3) that result from changes in market shares within therapeutic subgroups (ATC level 4) (Eq. (4)). Similarly, the drug mix measure captures the changes in expenditures at the therapeutic subgroup level (ATC level 4) resulting from changes in market shares at the active ingredient level (ATC level 5) (Eq. (5)). In the context of diabetes drugs, for example, if the relatively more expensive DPP-4 inhibitors capture market share from the less expensive TZDs, it would result in an increase in the therapeutic mix measure. In turn, changes in market shares between two different types of TZDs would be reflected as a change in the drug mix measure.

$$\Delta Therapeutic\ mix = \frac{\sqrt{\frac{\sum C^t_{atc3P} Q^0_{atc3P}}{\sum C^0_{atc3P} Q^0_{atc3P}} \times \frac{\sum C^t_{atc3P} Q^t_{atc3P}}{\sum C^0_{atc3P} Q^t_{atc3P}}}}{\sqrt{\frac{\sum C^t_{atc4P} Q^0_{atc4P}}{\sum C^0_{atc4P} Q^0_{atc4P}} \times \frac{\sum C^t_{atc4P} Q^t_{atc4P}}{\sum C^0_{atc4P} Q^t_{atc4P}}}} \quad (4)$$

$$\Delta Drug\ mix = \frac{\sqrt{\frac{\sum C^t_{atc4P} Q^0_{atc4P}}{\sum C^0_{atc4P} Q^0_{atc4P}} \times \frac{\sum C^t_{atc4P} Q^t_{atc4P}}{\sum C^0_{atc4P} Q^t_{atc4P}}}}{\sqrt{\frac{\sum C^t_{atc5P} Q^0_{atc5P}}{\sum C^0_{atc5P} Q^0_{atc5P}} \times \frac{\sum C^t_{atc5P} Q^t_{atc5P}}{\sum C^0_{atc5P} Q^t_{atc5P}}}} \quad (5)$$

where C_{atc4P} and Q_{atc4P} are aggregate expenditure and number of purchases at ATC level 4. There are 4 observations for insulins and 5 observations for non-insulins at this level (see tables 7 and 8 in the appendix).

2.6. Price effects

According to Morgan [21], "price effects are factors that directly affect the cost of selected drugs". Price effects thus include changes in the retail prices of products on the market (price changes) and changes in the average unit cost that derive from switches between products within the same active ingredient category (product mix). Changes in product mix may result from price competition between originator and (branded) generic products, e.g., due to generic substitution and reference pricing. In our analysis, price changes were measured with a price index aggregated at package level measuring the change in cost per DDD for all products (Eq. (6)). The product mix was measured with an expenditure weighted average of changes in the unit costs at active ingredient level (ATC level 5), resulting from changes in the market shares at the package level (Eq. (7)).

$$\Delta Price\ changes = \sqrt{\frac{\sum C^t_{packU} Q^0_{packU}}{\sum C^0_{packU} Q^0_{packU}} \times \frac{\sum C^t_{packU} Q^t_{packU}}{\sum C^0_{packU} Q^t_{packU}}} \quad (6)$$

$$\Delta Product\ mix = \frac{\sqrt{\frac{\sum C^t_{atc5U} Q^0_{atc5U}}{\sum C^0_{atc5U} Q^0_{atc5U}} \times \frac{\sum C^t_{atc5U} Q^t_{atc5U}}{\sum C^0_{atc5U} Q^t_{atc5U}}}}{\sqrt{\frac{\sum C^t_{packU} Q^0_{packU}}{\sum C^0_{packU} Q^0_{packU}} \times \frac{\sum C^t_{packU} Q^t_{packU}}{\sum C^0_{packU} Q^t_{packU}}}} \quad (7)$$

where C_{packU} and Q_{packU} are aggregate cost per DDD and number of DDDs at package level. There are 109 unique packages for insulins

Table 1
Changes in total costs, costs per capita, number of purchases and total number of DDDs of insulins and non-insulins, 2003 to 2015.

Year	Insulin				Non-insulin			
	Total costs (€)	Cost per capita (€)	Number of purchases	Number of DDDs	Total costs (€)	Cost per capita (€)	Number of purchases	Number of DDDs
2003	52 million	10.07	397,500	35 million	33 million	6.39	643,945	67 million
2004	62 million	11.79	398,715	37 million	38 million	7.21	703,042	75 million
2005	67 million	12.74	403,895	38 million	42 million	8.06	758,327	81 million
2006	68 million	12.93	411,834	40 million	40 million	7.54	808,207	85 million
2007	77 million	14.53	439,331	45 million	42 million	7.88	879,602	91 million
2008	86 million	16.27	469,644	49 million	44 million	8.37	999,607	98 million
2009	97 million	18.26	488,518	53 million	48 million	9.06	1,065,160	101 million
2010	106 million	19.80	505,223	56 million	62 million	11.64	1,129,280	106 million
2011	108 million	20.10	509,959	57 million	73 million	13.65	1,159,895	109 million
2012	107 million	19.84	514,677	58 million	83 million	15.35	1,206,571	113 million
2013	104 million	19.20	522,972	59 million	89 million	16.38	1,255,267	116 million
2014	101 million	18.44	536,834	60 million	98 million	18.02	1,322,792	120 million
2015	102 million	18.71	555,778	61 million	110 million	20.12	1,512,249	126 million
Nominal change 2003-2015	50 million	8.64	158,278	26 million	77 million	13.73	868,304	58 million
2003-2015 change in %	95 %	86 %	40 %	73 %	231 %	215 %	135 %	87 %

and 322 unique packages for non-insulins at this level (see tables 7 and 8 in the appendix).

All analyses were conducted using R software version 3.4.4 [33].

3. Results

From 2003 to 2015, the annual number of insulin purchases increased from 397,550 to 555,778 (40%), the number of annually purchased DDDs increased from 35 million to 61 million (73%) and the per capita expenditure on insulins from €10.07 to €18.71 (86%) (Table 1). For non-insulins, the number of purchases increased from 643,945 to 1,512,249 (135%), the number of annually purchased DDDs increased from 67 million to 126 million (87%) and the per capita expenditure from €6.39 to €20.12 (215%). The increases in per capita expenditures translate into increases of €50 million and €77 million in the total expenditures for insulins and non-insulins respectively. Due to the larger cost increase in the non-insulin category, the total cost of non-insulin surpassed the total costs of insulins by 2015.

From 2003 to 2015, the number of DDDs per user increased for insulins from 461 to 505 (10%), and decreased for non-insulins from 500 to 415 (−17%) (Table 2). The average cost per user increased from €682.27 to €841.80 (23%) for insulins and from €247.31 to €363.89 (47%) for non-insulins. The prevalence of insulin users per 1000 inhabitants increased from 14.8 to 22.2 and of non-insulin users from 25.9 to 55.3.

3.1. Decomposition results for insulins

The largest increase in per capita expenditures resulted from changes in purchase volume (Table 3). The number of insulin purchases increased by 158,278, which accounted for €4.67 or 40% out of the total increase in per capita expenditures (€8.64 or 86%). Changes in purchase size increased the per capita expenditure by €4.33 or 36%.

Changes in therapeutic mix had the third largest impact on per capita expenditures (Table 3). The therapeutic mix determinant, measuring changes in the market shares between the chemical subgroups at ATC level 4 within the A10A class, accounted for €4.07 or a 34% increase in per capita expenditure. This increase captures the shift in use from intermediate acting insulins and mixed insulins towards newer long-acting insulins (Table 4). Drug mix, which measures changes in the market shares at ATC level 5 within the ATC level 4, had a modest but increasing effect on the per capita expenditure accounting for an increase of €0.40 or 3% in per capita expenditures.

Price effects, including changes in prices and changes in product mix, had a decreasing effect on per capita expenditures (Table 3). Based on the price index, which measures changes in cost per DDD

Table 2
Changes in prevalence and per user statistics of insulins and non-insulins, 2003 to 2015.

Year	Insulin				Non-insulin			
	Number of users per 1000 inhabitants	Average number of purchases per user	Average number of DDDs per user	Average cost per user (€)	Number of users per 1000 inhabitants	Average number of purchases per user	Average number of DDDs per user	Average cost per user (€)
2003	14.8	5.17	460.5	682.27	25.9	4.78	499.7	247.31
2004	15.4	4.95	454.5	764.46	28.2	4.78	507.6	255.81
2005	16.0	4.81	458.4	794.56	30.3	4.79	513.2	266.36
2006	16.6	4.73	464.5	780.51	32.2	4.77	504.8	233.87
2007	17.6	4.72	479.5	823.40	35.7	4.67	484.5	220.68
2008	18.6	4.76	498.1	873.82	40.3	4.68	457.5	207.79
2009	19.5	4.72	509.7	938.83	43.4	4.61	435.5	208.66
2010	20.1	4.69	519.0	982.69	46.3	4.56	428.8	251.45
2011	20.7	4.59	517.5	972.43	48.2	4.48	422.8	283.55
2012	21.1	4.52	512.9	940.96	49.9	4.48	420.1	307.69
2013	21.6	4.47	508.0	890.10	51.9	4.45	411.2	315.39
2014	21.9	4.49	504.2	840.78	53.7	4.52	410.9	335.54
2015	22.2	4.57	504.6	841.80	55.3	5.00	415.3	363.89
Nominal change 2003-2015	7.5	−0.6	44.1	159.53	29.4	0.2	−84.4	116.58
2003-2015 change in %	51%	−12%	10%	23%	114%	5%	−17%	47%

Table 3
Determinants of change in per capita expenditures for insulins and non-insulins, 2003-2015.

	Insulins		Non-insulins	
2003 per capita expenditure	€10.07		€6.39	
2015 per capita expenditure	€18.71		€20.12	
Total change	**€8.64**	**86%**	**€13.73**	**215%**
Purchase volume	€4.67	40%	€10.22	135%
Purchase size	€4.33	36%	€1.48	13%
Volume effects	**€9.00**	**91%**	**€11.71**	**166%**
Therapeutic mix	€4.07	34%	€10.17	134%
Drug mix	€0.40	3%	-€0.70	−6%
Therapeutic choices	**€4.47**	**38%**	**€9.47**	**121%**
Price changes	-€2.37	−16%	-€6.22	−41%
Product mix	-€2.47	−16%	-€1.23	−10%
Price effects	**-€4.83**	**−29%**	**-€7.45**	**−46%**

Note: Percentage values are based on index values and their relationship is multiplicative e.g. Purchase volume * Purchase size = 1.398 * 1.364 = 1.907 = Volume effects (insulins). All index values are listed in the appendix (see tables 5 and 6). Euro values are derived from a logarithmic transformation of the index decomposition and their relationship is additive. For detailed description of the logarithmic decomposition see the appendix of [14]. All cost are in 2015 euros.

for insulin products, the per capita expenditure was €2.37 or 16% less than it would have been if the prices remained at 2003 levels. Changes in product mix, measuring the impact of shifting towards cheaper (or more expensive) products within the categories at the active ingredient level of the ATC system, accounted for a decrease of €2.47 or 16% in per capita expenditures.

3.2. Decomposition results for non-insulins

The largest increase in per capita expenditures on non-insulins resulted from changes in the purchase volume. The number of purchases of non-insulin increased by 868,304 purchases, which accounted for an increase of €10.22 or 135% out of the total change in per capita expenditure (€13.73 or 215%) (Table 3). The second largest increase resulted from changes in therapeutic mix accounting for €10.17 or 134%. This includes the cost increasing effects of sulfonylureas and thiazolidinediones being replaced by DPP-4 inhibitors, which accounted for approximately 60% of the total non-insulin expenditure by 2015 (Table 4). Additionally, by 2015, the newest therapeutic group GLP-1 analogues had a similar expenditure share with metformin even though the consumption of metformin, measured in DDDs, was approximately 13 times higher (Table 4). The change in purchase size increased per capita expenditure by €1.48 or 13%.

Differing from insulins, the drug mix decreased the per capita expenditure on non-insulins by €0.70 or 6% (Table 3). Changes in price had a decreasing effect on per capita expenditures. The decreasing trend in cost per DDD translates to a decrease of €6.22 or 41% in expenditures per capita. Changes in product mix decreased per capita expenditures by €1.23 or 10%.

The results of the sensitivity analysis where combination products were treated as a separate group of products are listed in Appendix Table 9. These results suggest that purchase size and product mix are the most sensitive to different treatments of combination products in the analysis. The decreasing impact of product mix was €0.66 less in the sensitivity analysis compared to the main analysis (−€0,57 vs. −€1.23, respectively). In turn, the increasing impact of purchase size was €0.65 less in the sensitivity analysis compared to the main analysis (€0.83 vs. €1.48, respectively). Differences in other determinants were negligible between the main analysis and sensitivity analysis. Overall, the results of the sensitivity analysis did not change the conclusions of our study.

4. Discussion

From 2003–2015, the per capita diabetes drug expenditure increased by 86% (€8.64) for insulins and by 215% (€13.73) for non-insulins. The main drivers of expenditure growth in both drug classes were increases in the number and size of purchases, and a shift in use towards newer and more expensive drugs. Prices, however, had a decreasing effect on expenditure. Although the main components explaining expenditure growth were the same for insulins and non-insulins, there were important differences in their order and magnitude.

For insulins, the largest components of expenditure growth were the increase in the number of purchases together with increases in the average number of DDDs per purchase. These findings suggest that both the number of people with insulin purchases and their insulin doses have increased between 2003 and 2015. Possible reasons for these trends include the increasing prevalence of type 2 diabetes and its risk factors, changes in treatment patterns towards insulin use and towards higher insulin doses because of, e.g., the ageing and obesity of the diabetes population [1,11,34]. Nevertheless, one could argue that the changes in the dispensing sizes might be merely due to people changing their purchase behavior. However, both dispensing size and interval are strictly monitored, and the co-payment system strongly incentivizes patients' to fill the entire three months' supply per dispensing. Therefore, in the Finnish context, an increase in purchase size is a relatively reliable indication of growth in the three-month equivalent number of DDDs. Furthermore, the shift in use from intermediate acting insulins and mixed insulins towards newer long-acting insulins showed a significant contribution to the expenditure increase. Of note, it is possible that the shift between formulations has also contributed to the increase in doses used, because of the differences in the safety profile and changes in the user base of the products. A decreasing price trend, as well as increasing use of lower price packages, resulted in moderate cost savings.

For non-insulins, an important component of the expenditure increase was a change in therapeutic choices, meaning that dur-

Table 4
Changes in expenditure shares and in quantity of purchased DDDs, 2003 to 2015.

Insulin / Non-insulin	Quantity of purchased Defined Daily Doses (DDDs) in 2003	Expenditure share in 2003	Quantity of Defined Daily Doses (DDDs) in 2015	Expenditure share in 2015
Fast-acting insulin	8 million	25%	18 million	22%
Intermediate-acting insulin	21 million	55%	2 million	2%
Mixed insulin	5 million	15%	1 million	2%
Long-acting insulin	0.9 million	5%	40 million	74%
Biguanides (metformin)	25 million	41%	75 million	18%
Sulfonylureas	41 million	55%	6 million	1%
Thiazolidinediones	0.3 million	3%	2 million	1%
Dipeptidyl peptidase 4 (DPP-4) inhibitors	0 million	0%	37 million	62%
Other blood glucose lowering drugs (i.a. GLP-1), excl. insulins	0.09 million	0%	6 million	18%

ing the study period, newer and more expensive products, mainly DPP-4 inhibitors and GLP-1 analogues, have captured market share from the older products. It is also noteworthy that even though metformin is the most used non-insulin diabetes drug, its expenditure share has decreased since 2009, because of decreasing prices due to the price competition caused by the reference price system, and the increasing use of metformin as a part of combination products. Furthermore, increases in the number of non-insulin purchases contributed significantly to expenditure growth. The increased average number of DDDs per purchase had an increasing impact on the non-insulin expenditure growth as well, but its magnitude was lower than with insulins. The results indicate that the decreasing price trend and substitutions to lower cost alternatives at both the package level and the active ingredient level decreased the diabetes drug expenditure. However, the size of the decreasing cost impact of substitutions to lower cost alternatives should be interpreted with caution, since this result was the most sensitive to treatment of combination products in the analysis.

The use of newer and more expensive products has also been identified in previous studies as a significant cost driver in many drug classes [16,21,22]. Accordingly, our study illustrated the impact of the use of newer drugs on diabetes drug expenditure. Shifts in use towards newer antidiabetic agents, such as DPP-4 inhibitors, have been previously reported from other countries [35,36]. Possible explanations for the rapid uptake of new diabetes drugs in Finland are the lack of economic considerations in the Finnish clinical guidelines and lack of incentives for cost-conscious prescribing [37]. Furthermore, after inclusion in the higher reimbursement category, diabetes drugs were, at the time of study, reimbursed at a particularly high rate in the Finnish context, and thus, unlike for many other drug classes, patients' ability to pay was not likely to influence prescriber drug choices. Additionally, a large national program for the prevention and care of diabetes, DEHKO, was carried out in Finland during 2000–2010, which may also have affected therapeutic choices [38].

Previous research has reported both increasing and decreasing effects of prices on drug expenditure [17,18,21]. In Finland, the drug market is highly regulated, and increases in prices are extremely rare. Thus, the observed decreasing effect of prices on drug expenditure was expected. The policies adopted to control expenditure growth are the likely explanation for the price decrease being larger for non-insulins than insulins. For example in 2015, metformin, glimepiride, pioglitazone and repaglinide were subject to generic substitution and included in the reference price system [39], which is likely to have increased price competition between products and steered purchases towards lower cost alternatives. Insulins, conversely, do not face similar price competition since they are parenterally administered biopharmaceuticals [40]. In fact, between 2003 and 2015 there were no biosimilar insulin products available in the Finnish pharmaceutical market and therefore insulins are not subject to generic substitution in Finland. Given this framework for competition in the insulin market, the decreasing price effects are presumably to a large extent the result of two government savings reforms which included cutting the wholesale prices of reimbursed products by 5%, in 2006 and 2013.

Changes in therapeutic choices and an increase in the number of purchases were observed for both insulins and non-insulins. From the perspective of rational use of public resources, as long as the increase in demand for drug therapy reflects fulfillment of increased medical need and helps to ensure good quality of life and prevent complications associated with diabetes, it can be regarded as an acceptable expenditure increase. Ensuring access to cost-effective drug treatment might result in savings in total health care costs, since complications and hospitalizations are the main reason for the high cost of diabetes care [38,41]. Regarding therapeutic choices, it is unclear and out of the scope of this study whether the use of these newer drugs has led to improvements in treatment outcomes. OECD data reveals that hospital admissions for diabetes have decreased from 2008 to 2013 in Finland [1]. Hospital admissions for diabetes have also decreased in Sweden (−5%), Denmark (−5%) and Norway (−5%), but the decrease is slightly larger in Finland (−7%) [1]. The extent to which this has been due to the use of newer drugs is, however, not obvious and requires further research. In general, given the significant impact of therapeutic choices on drug expenditure, careful economic evaluations are required to ensure that investments in the use of newer drugs result in proportionate improvements in treatment outcomes.

The results of the present study are in line with the findings from previous decomposition studies of drug expenditure in the sense that volume effects and therapeutic choices have been the main forces driving drug expenditures. Despite the decreasing effects of price components, their effects have been counterbalanced by the increases caused by the other components [16,18,21,22]. The higher average unit cost of insulins than non-insulins underlines the potential cost savings that might be expected from a larger scale introduction of biosimilars. In terms of controlling expenditure on non-insulins, future cost containment measures should concentrate on the non-price components of drug expenditure.

4.1. Strengths and limitations

This study was based on a national register containing the complete reimbursed outpatient sales data on drugs used in the treatment of diabetes in Finland during the 13-year period of 2003–2015. For example, in 2015 the consumption of insulin in our data is 30.73 DDDs/1000 inhabitants/day, whereas the Finnish drug consumption statistics report 31.72 DDDs/1000 inhabitants/day for out-patient setting. Similarly, non-insulin consumption is 62.93 DDDs/1000 inhabitants/day in our data vs. 58.35 DDDs/1000 inhabitants/day in Finnish drug consumption statistics for outpatient setting [42]. Thus, it should be noted that the indexes constructed in this study are not based on a sample but the whole population.

However, a few caveats should be noted. First, diagnostic information was not comprehensively registered in the data and therefore it was not known whether the drugs were purchased for treating type 1 or type 2 diabetes. Including this information in the analysis would have broadened the understanding of diabetes drug expenditure, especially in the insulin category. Second, it is also noteworthy that DDD is a statistical unit and as such does not necessarily represent prescribed doses. For example, the DDD for metformin is 2 g, but the Finnish clinical guidelines recommend doses up to 3 g per day [41]. However, since actual prescribed doses were not included in the data, DDDs were the best available unit for this study, since they standardized purchases of products with different formulations, strengths and package sizes. The cost impact of the changes in patient's actual doses requires further research. Finally, we did not have information on the diabetes drugs administered in hospitals or other institutions. However, the amount of diabetes drugs sold to institutions is only approximately 2% of all sales of antidiabetic agents measured in wholesale prices [43].

5. Conclusions

The main driving forces behind the increasing diabetes drug expenditure were an increase in the number of purchases of antidiabetic agents, an increase in the size of those purchases and a change towards newer and more expensive alternatives in therapeutic choices. Prices and substitutions to cheaper packages have had a decreasing effect on diabetes drug expenditure, but their impact was modest in comparison to the increase caused by other components.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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