Medication use in public pharmacies

Opiates

Analysis of the distribution and evolution of medication consumption in Belgium, in terms of volume and expenditure per insured (analysis and trends by region, province and district), for the year **2021**

NIHDI – Healthcare Service – Directorate for Research, Development and Quality promotion

Appropriate care unit

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Date of report: 28 October 2022

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1. INTRODUCTION

The Appropriate Care Unit was set up within the NIHDI's Directorate for Research, Development and Quality under NIHDI's Administration Contract for 2016-2018[1]. Article 35 of this contract refers to 'the setting up of an Appropriate Care Unit, aiming specifically to promote an integrated approach to the rational use of resources'. The Appropriate Care Unit has been up and running since the second quarter of 2017.

The tasks of the Unit were set out formally in the '2016-2017 Healthcare monitoring Action plan', published by NIHDI on 18 July 2016[2]. This plan lists around thirty measures designed to make healthcare provision more efficient, by encouraging appropriate practice and tackling unnecessary or inappropriate care.

The plan states that one of the tasks of the Appropriate Care Unit is to analyse the 'appropriateness of care', in order to identify unexplained variations in consumption patterns, identified after standardisation. Such variations can potentially point to non-optimal use of resources.

"Medication use" documents report on the analyses carried out in this framework. Each report focuses on a particular topic.

In this document, we present the figures and graphs relating to analyses[3] of opiate use, and give the explanations necessary to understand these.

We have deliberately chosen not to attempt to interpret the figures, preferring to present the results to experts who are in a better position to do so. This document has nevertheless been made available to the public in order to provide objective, open input to discussions on this issue.

[1] (Institut national d'assurance maladie-invalidité, 2016)
[2] (Institut national d'assurance maladie-invalidité, 2016)
[3] Readers interested in the methodology used in these quantitative analyses should consult the document entitled 'Variations in practice – Methodology'.

2. METHODOLOGY

A. ATC codes (Anatomical Therapeutic Chemical Classification System) selected for this analysis

The ATC codes selected for the analysis are listed below:

Code_atc	Atc_FR	Code_atc_5	Atc_5_FR	Taux	Dépenses	Cheap existe	CodeGroup1
N02AA01	MORPHINE	N02AA	ALCALOIDES NATURELS DE L'OPIUM	oui	oui	oui	6_Autre_opioide
N02AA03	HYDROMORPHONE	N02AA	ALCALOIDES NATURELS DE L'OPIUM	oui	oui	non	6_Autre_opioide
N02AA05	OXYCODONE	N02AA	ALCALOIDES NATURELS DE L'OPIUM	oui	oui	oui	1_OXYCODONE
N02AB03	FENTANYL	N02AB	DERIVES DE LA PHENYLPIPERIDINE	oui	oui	oui	2_FENTANYL
N02AC03	PIRITRAMIDE	N02AC	DERIVES DE LA DIPHENYLPROPYLAMINE	oui	oui	non	6_Autre_opioide
N02AE01	BUPRENORPHINE	N02AE	DERIVES DE L'ORIPAVINE	oui	oui	oui	6_Autre_opioide
N02AJ13	TRAMADOL ET PARACETAMOL	N02AJ	OPIOIDES AVEC DES ANALGESIQUES NON-OPIOIDES	oui	oui	oui	3_TRAMADOL
N02AX01	TILIDINE	N02AX	AUTRES OPIOIDES	oui	oui	non	4_TILIDINE
N02AX02	TRAMADOL	N02AX	AUTRES OPIOIDES	oui	oui	oui	5_TRAMADOL
N02AX06	TAPENTADOL	N02AX	AUTRES OPIOIDES	oui	oui	non	6_Autre_opioide

This table shows the ATC codes selected for this analysis, stating whether or not they were included in the analyses of prescriptions and expenditure, and giving, for each one, a description, dates of creation and deletion, where appropriate, their N group (in the NIHDI nomenclature) and their value.

B. Source of data and analysis period

The data used in the analyses have been taken from the following databases:

Pharmanet document	For the utilisation rate (medication use in DDD per 100,000 insured) and amount of expenses of insured persons (who meet the selection criteria) whose age, sex, preferential regime and district are known in 2011-2021. The data are collected per accounting period.

Analysis period	2011-2021

Pharmanet documents: Pharmanet documents are data from public pharmacies communicated by the invoice offices within the framework of the health care insurance. These data show the information of the prescriptions issued, namely the identifier of the substance issued, the number of packages, the date of sale, an encrypted patient code and the prescriber code. **These data mainly concern medicines reimbursed under the health insurance scheme**
Packaging is converted into DDD (Defined Daily Dose) according to the references of the World Health Organization.
Cheap drugs are identified on the basis of their CNK code (The CNK code is a unique identification number per package, assigned to all drugs and para-pharmaceuticals (medical devices, food supplements, cosmetics ...) delivered in pharmacies.
Pharmanet also provides the following information on patients: can be retrieved: age, gender, social category and district of residence.
Cross-referencing the prescriber code with NIHDI data allows the prescriber's specialty to be retrieved.
Finally, the comparison of Pharmanet with IQVIA data (which are the sales of wholesalers to public pharmacies) converted into DDD allows to estimate the approximate share of medicines delivered outside insurance.

C. Specific selection criteria

Several filters may have been applied to the data, so that only one section of the population is considered in the analyses. If so, the filters used are shown in the table below:

FILTERS APPLIED TO DATA	
Sex	all
Age	all
-	-

D. Standardisation

The data are standardised before analysis per year, based on age, sex and preferential regime per district, province and region (standardization based on population in 2021).

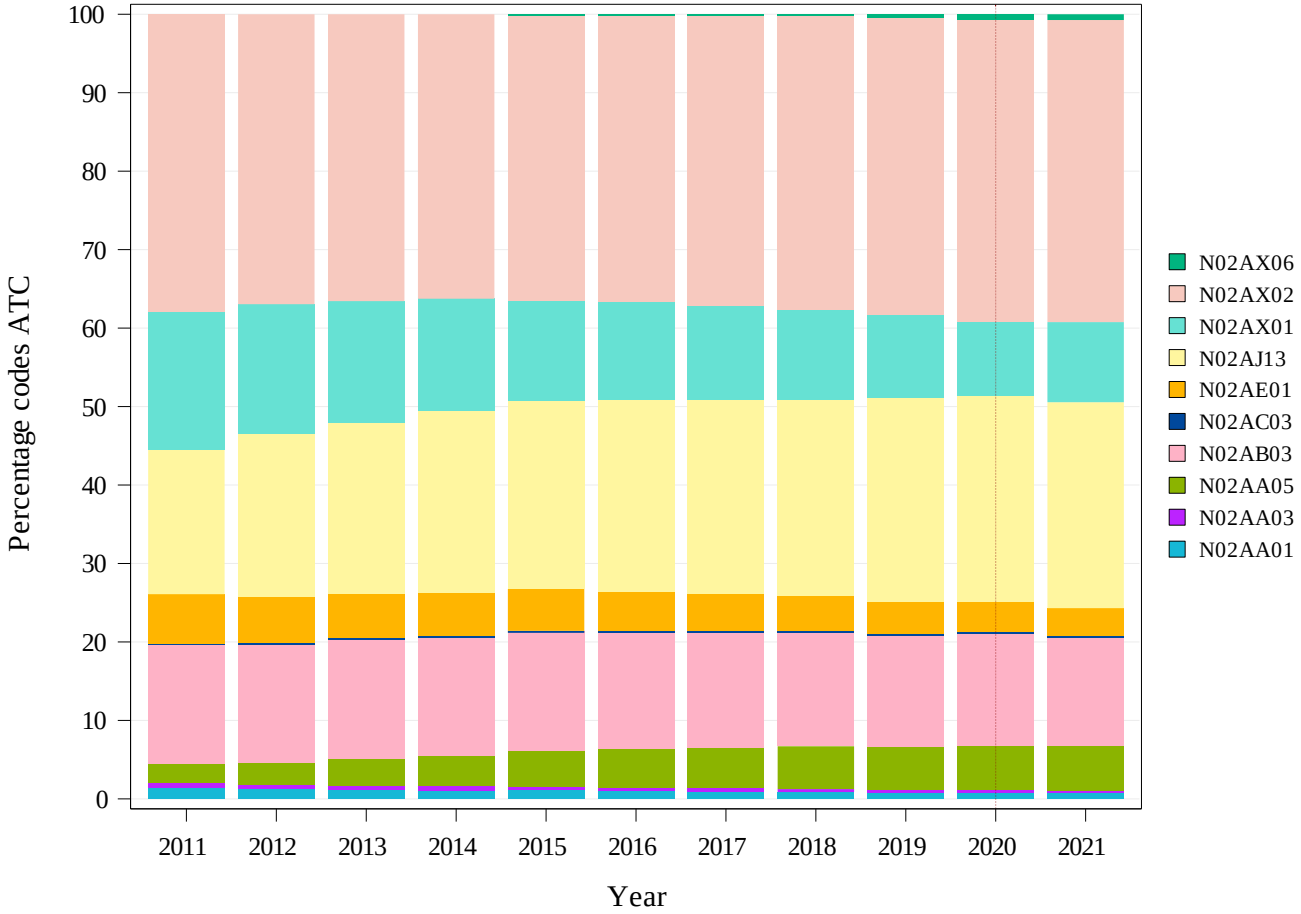
Standardisation renders populations comparable in relation to one or several criteria. If a difference is observed between these populations, we can therefore assume that it is not due to the criteria covered by the standardisation process.

3. RESULTS

A. National standardised rate of use (2021)

	TOTAL
Consumption of medicines per year (DDD)	70.049.749
Standardised rate of use per 100 000 insured persons (consumption of medicines delivered converted into DDD)	610.978

B. Distribution of ATC codes delivered in terms of volume (DDD)



See the ATC codes (Anatomical Therapeutic Chemical Classification System) selected for this analysis on page 4 for further information.
Note : The year 2020 was highlighted by a vertical dashed line, in order to draw the attention on the impact of the COVID-19 crisis

C. Specialisation of prescribers

Specialisation of the prescriber	Total prescribers	Concerned prescribers	% Prescribers	Median of prescribed DDD	Q3 of prescribed DDD	P90 of prescribed DDD	Volume of prescribed DDD	% DDD	% DDD cheap	Expenses	% Expenses
General practitioners	19.139	14.759	77%	2.462,00	5.440,29	9.290,61	56.055.688,00	80,03%	86,64%	43.969.921,25	78,19%
General practitioners in training	6.206	3.965	64%	383,00	1.215,38	2.401,27	3.496.536,00	4,99%	87,72%	2.807.090,62	4,99%
Specialists in training	11.311	6.381	56%	114,00	375,00	856,03	1.994.946,00	2,85%	93,97%	2.096.432,71	3,73%
Orthopedical surgery	1.441	1.132	79%	574,00	1.296,27	2.506,80	1.196.231,00	1,71%	93,27%	920.386,62	1,64%
Anesthesia-reanimation	2.861	1.426	50%	45,00	302,50	1.150,43	760.638,00	1,09%	83,10%	823.441,81	1,46%
Rheumatology	322	252	78%	1.410,00	3.560,38	6.564,72	755.671,00	1,08%	89,52%	457.646,54	0,81%
Other specialities	46.648	20.381	44%	149,00	365,55	798,92	5.785.293,00	8,26%	88,82%	5.156.461,98	9,17%
Total	87.928	48.296	55%	188,00	1.321,65	4.623,34	70.045.003,00	100,00%	87,19%	56.231.382,00	100,00%

This table shows, in order, the following non-standardised data per specialities (figures for the year 2021):

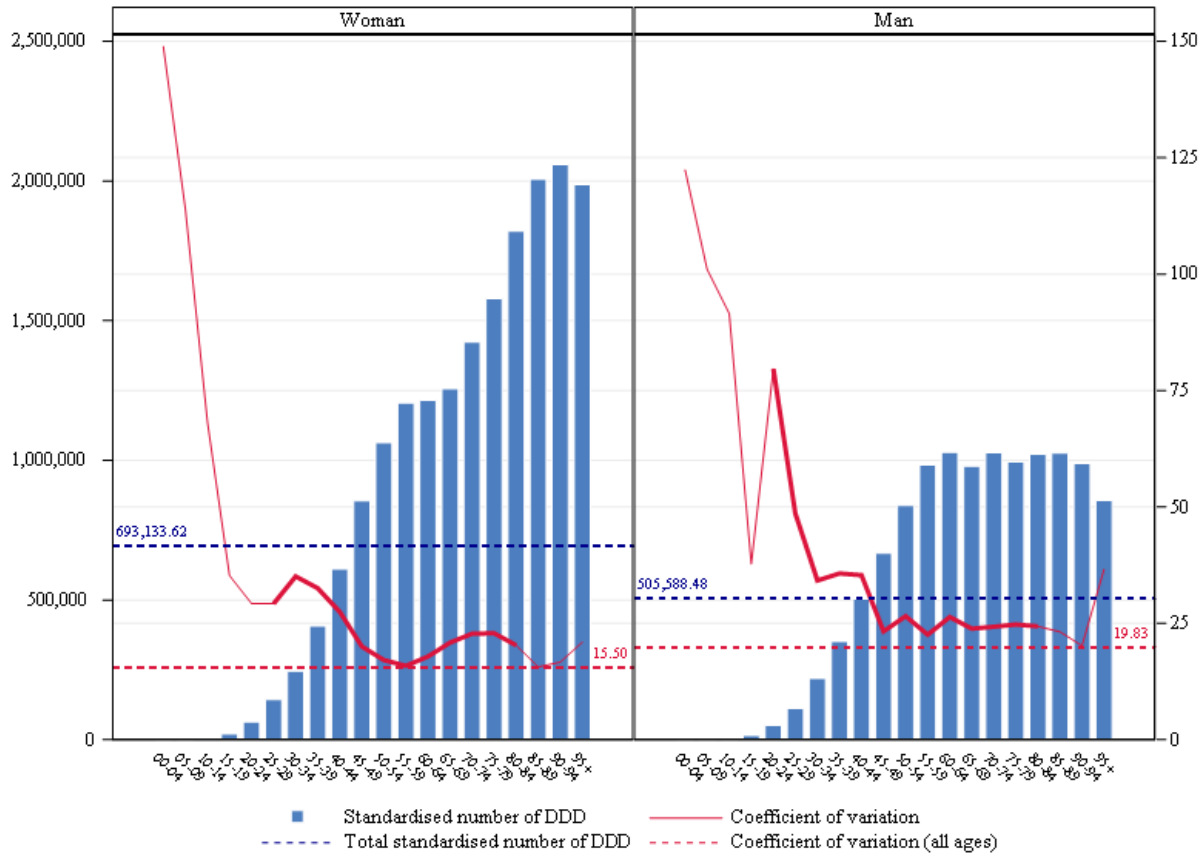
- The number of prescribers who prescribed at least one medicine delivered;
- The number of prescribers who prescribe the ATC codes selected for this analysis;
- The percentage of prescribers prescribing these codes out of the number of providers who prescribed at least one medicine delivered;
- The median number, third quartile (= 75th percentile) and 90th percentile of services per prescriber (prescribing codes);
- The percentage of medicines prescribed, i.e. the number of medicines prescribed for this specialisation as a percentage of total medicines prescribed;
- The percentage of low-cost drugs, i.e. the number of medicines identified as "cheap" per CNK code as a percentage of total medicines delivered;
- Expenditure refers to the total costs borne by insurance (excluding patient share and non-insurance sales);
- The percentage of expenditure is the share of this expenditure delivered by each prescriber group aggregated by specialty.

D. Standardised rate of use by sex and age group (consumption of medicines delivered converted into DDD per 100,000 insured)

	TOTAL
Consumption of medicines per year (DDD)	70.049.749
Median age (years)	63
Mean age (years)	63,1
Max/Min Ratio of the median age (by district)	1,12
Percentage of women	62,0%

Max/Min Ratio:

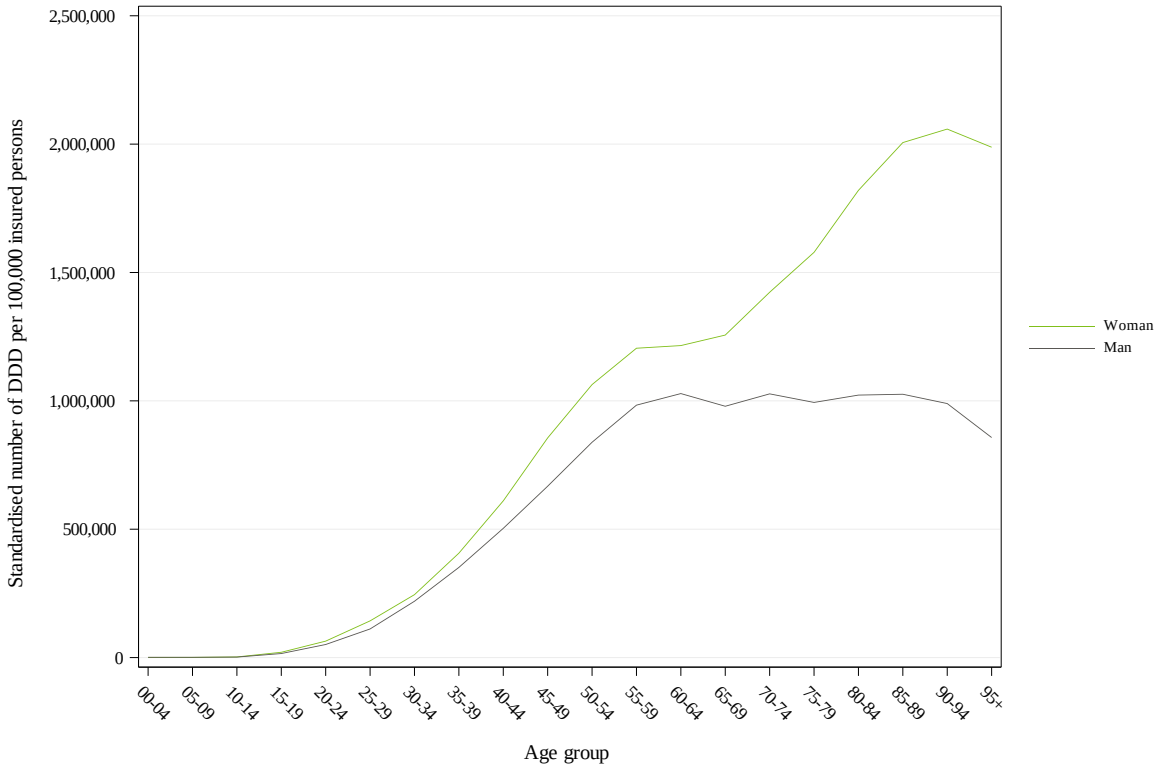
The max/min ratio measures the dispersion of values. It is calculated as the ratio of the maximum value found for the variable, in all districts, to the minimum value. If this minimum value is equal to zero, the max/min ratio cannot be calculated, and is reported as 'NA' ('not applicable').



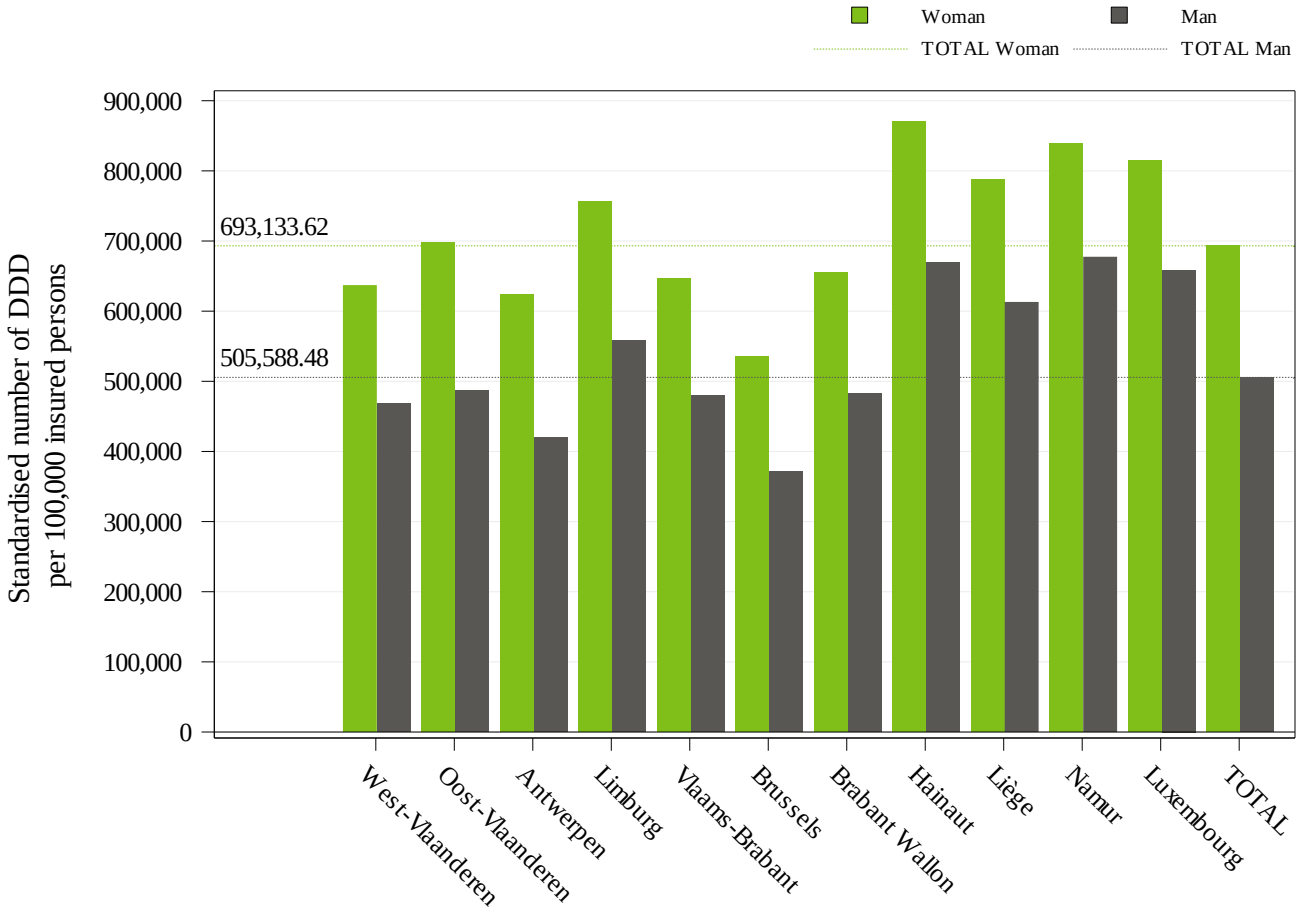
Standardised rate of use per 100 000 insured persons, and coefficient of variation for the districts, by age group and sex, for the year 2021

This figure is made up of bar charts for each sex. The **coefficient of variation**, shown by the red line, measures the relative dispersion of the standardised rates of use observed for each district, by age group and sex (standard deviation divided by the mean). This line is shown in bold for age groups where the coefficient of variation can be validly interpreted (i.e. for age groups in which there are sufficient insured persons per district to allow for a proper comparison).

The left-hand vertical axis of the graph represents the standardised rate of use, and the right-hand axis the coefficient of variation. The horizontal axis shows the age groups. The horizontal dotted lines show the total values of the standardised rates of use (in blue) and of the coefficient of variation (in red).



Comparison of the standardised rates of use by sex (per 100 000) in 2021

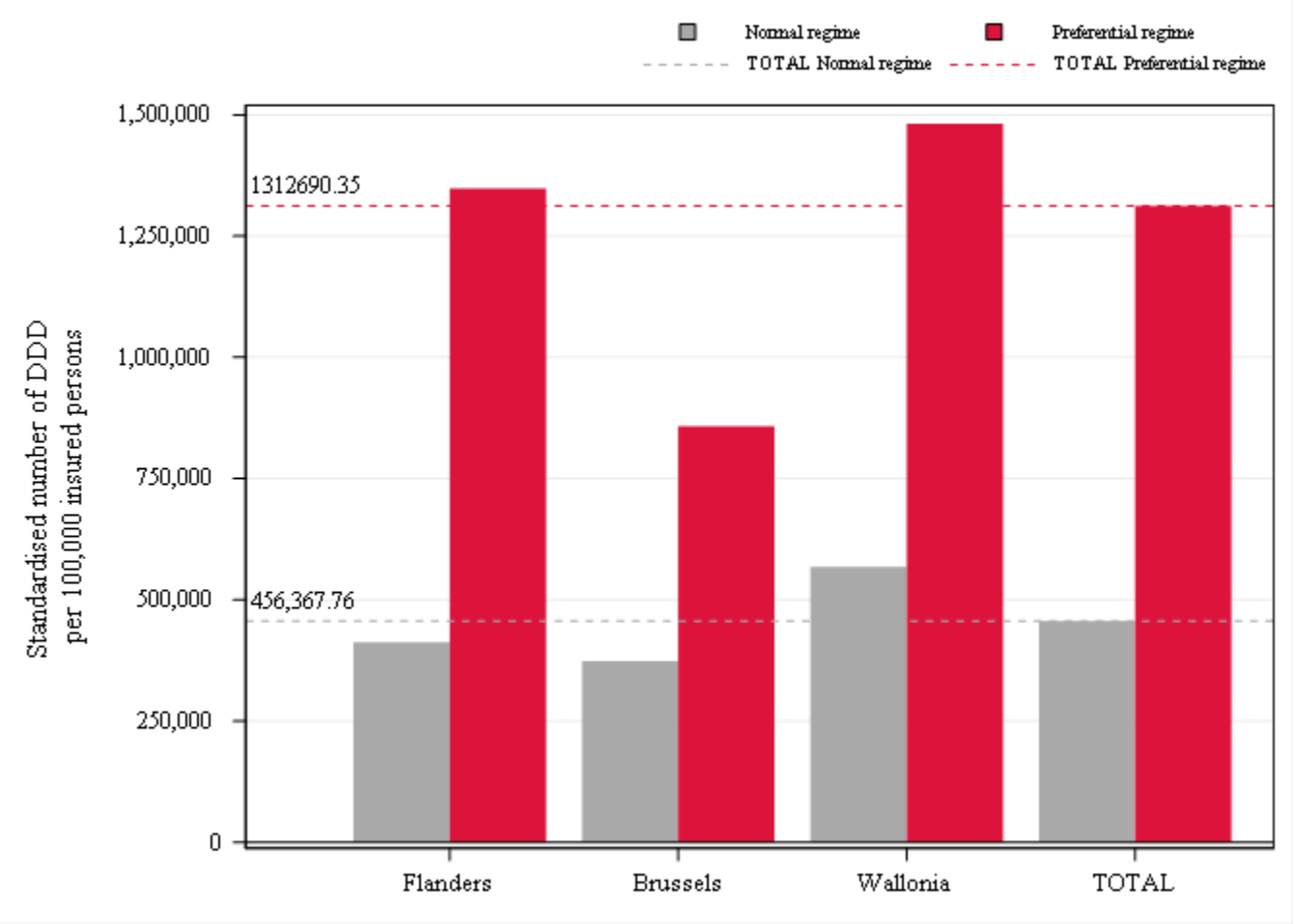


This histogram shows standardised rates of use by province and by sex. The grey bars show the rates for men, while the green bars show the rates for women, for each province. The grey and green broken lines show the total standardised rates of use, again grey for men, green for women.

Standardised rate of use per 100 000 insured persons, by sex and by province for the year 2021

E. Standardised rate of use by reimbursement scheme

	TOTAL
Annual consumption (DDD)	70.049.749
Percentage provided under the preferential reimbursement scheme	41,85%
Standardised rate of use with preferential reimbursement scheme (per 100 000)	1.312.690
Standardised rate of use without preferential reimbursement scheme (per 100 000)	456.368
Ratio Preferential scheme /General scheme	2,88



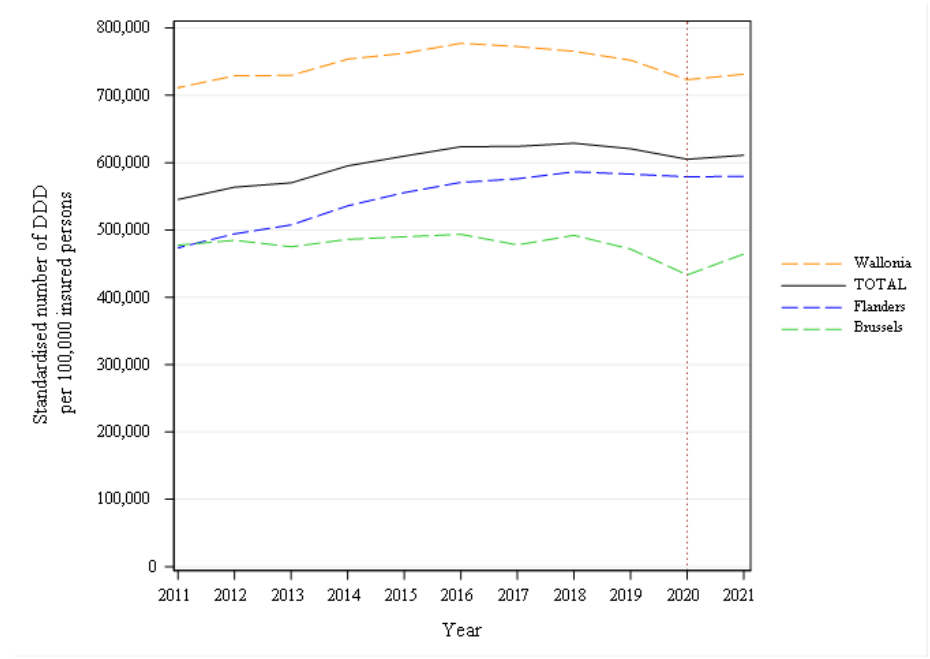
This graph shows the standardised rates of use with (in red) and without (in grey) the preferential reimbursement scheme, by region and in total. The red and grey dotted lines show the overall standardised rates of use, with and without the preferential reimbursement scheme, respectively.

Standardised rate of use by reimbursement scheme and by region

F. Trends in standardised rates of use

	TOTAL
Annual consumption (DDD)	**70.049.749**
Trend (2011-2021)	**1,14%**
Trend (2011-2019)	1,63%
Trend (2019-2021)	-0,78%

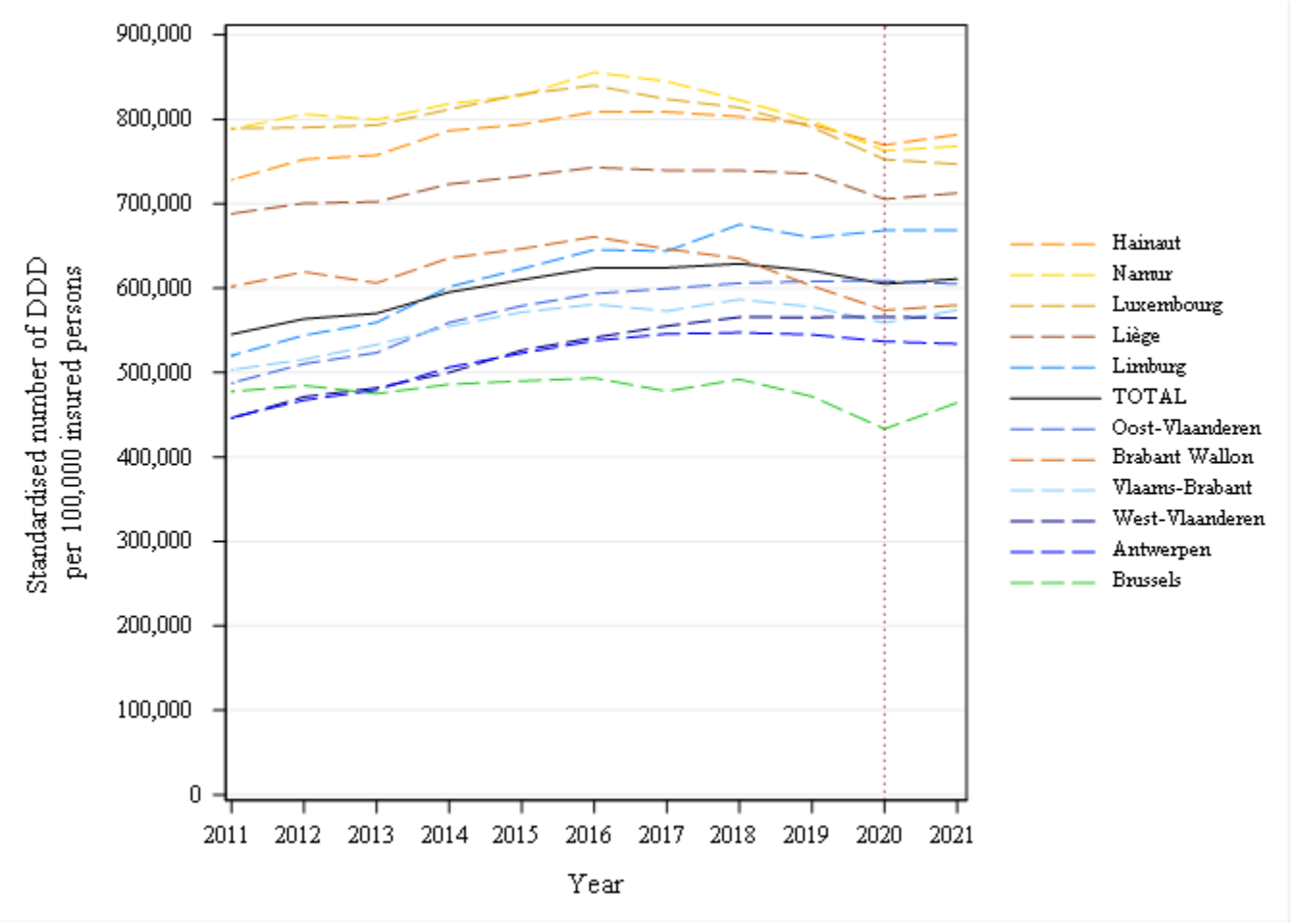
These trends correspond to the average annual growth rate.



This graph shows a coloured curve for each region and a black curve for the entire Belgian population. The x-axis shows the years, and the y-axis shows the standardised rate of use per 100 000 insured persons.

Note : The year 2020 was highlighted by a vertical dashed line, in order to draw the attention on the impact of the COVID-19 crisis.

Trends in the standardised rate of use per 100 000 insured persons, by region



This graph shows a colored line for each province and a black line for the entire Belgian population. The x-axis shows the years, and the y-axis shows the standardised rate of use per 100 000 insured persons.

Note : The year 2020 was highlighted by a vertical dashed line, in order to draw the attention on the impact of the COVID-19 crisis.

Trends in the standardised rate of use per 100 000 insured persons, by province

		Rate of use	Annual increase			
		2021 *(per 10^5 insured)*	2011-2021	2011-2019	2019-2021	Structural break
Provinces	West Flanders	564.604	2,40%	3,02%	-0,07%	NA
	East Flanders	604.938	2,18%	2,80%	-0,26%	NA
	Antwerp	533.973	1,80%	2,51%	-1,00%	NA
	Limburg	668.477	2,54%	3,02%	0,64%	NA
	Flemish Brabant	574.066	1,33%	1,74%	-0,32%	NA
	Brussels	464.268	-0,28%	-0,15%	-0,78%	NA
	Walloon Brabant	579.828	-0,37%	0,02%	-1,90%	NA
	Hainaut	781.848	0,72%	1,08%	-0,75%	NA
	Liège	712.522	0,35%	0,83%	-1,57%	NA
	Namur	768.040	-0,26%	0,15%	-1,89%	NA
	Luxembourg	746.916	-0,55%	0,03%	-2,81%	NA
Regions	Flanders	579.626	2,04%	2,63%	-0,29%	NA
	Brussels	464.268	-0,28%	-0,15%	-0,78%	NA
	Wallonia	731.361	0,28%	0,70%	-1,39%	NA
	TOTAL	**610.978**	**1,14%**	**1,63%**	**-0,78%**	***

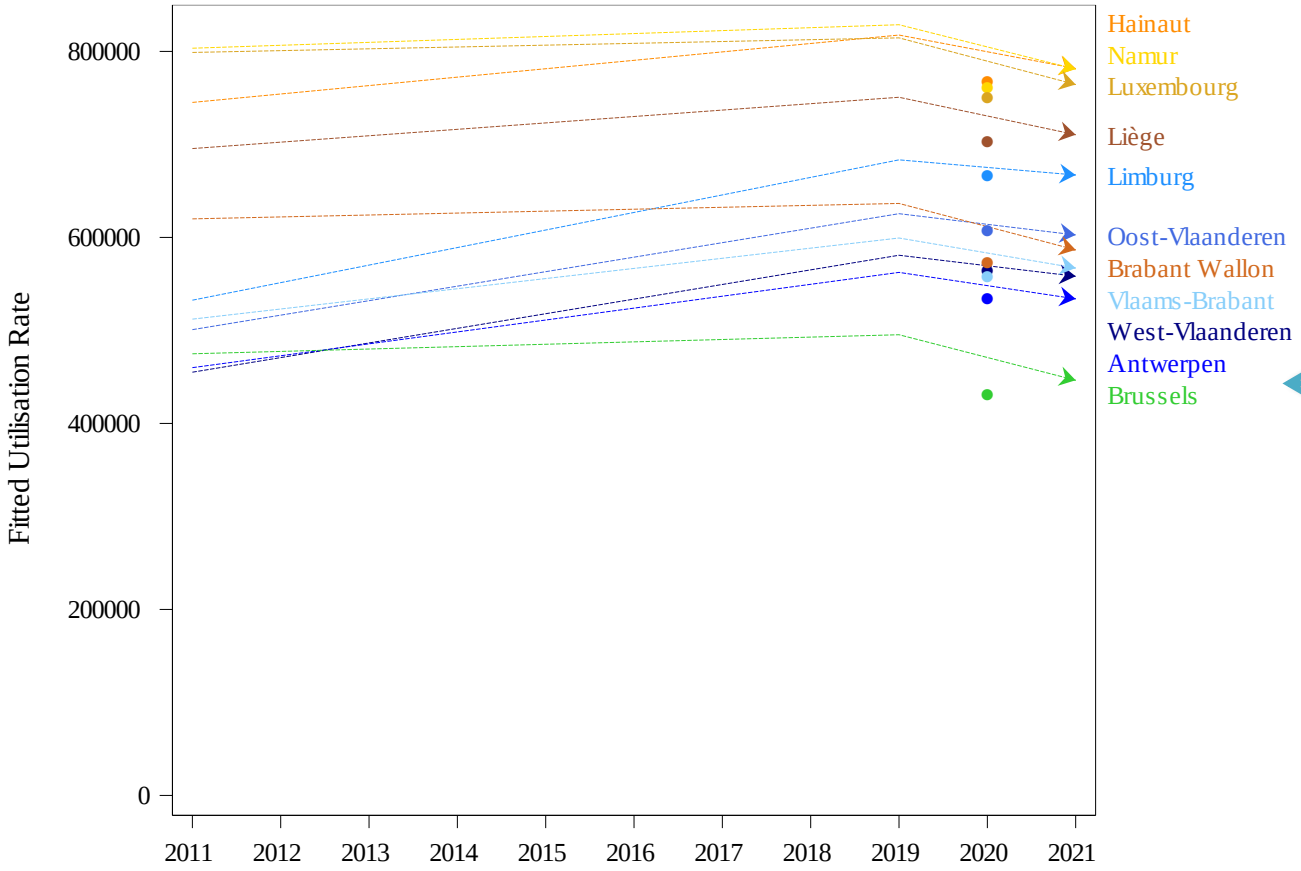
Trends in the rates of use, by province and region

This table reports the standardised **rates of use** (or consumption) for the last year analysed (2021), as well as the average **rates of increase**, by province, by region and in total, for the entire period (2011-2021), for the last three years (2019-2021) and for the period preceding the last three years (2011-2019).

In order to find out whether the trend in the last three years differs from that in the years before, a linear mixed model was fitted in two steps. In the first step a change in trend on the national level is tested. If this test is significant, in a second step, the model tests whether the difference in trend is significant for each province, region and at the national level. The data of 2020 are excluded from the models.

The significance of the test for a change in trend is reported in the Structural break column : * P-value ≤ 0.05 / ** P-value ≤ 0.01 / *** P-value ≤ 0.001 and NS for a non-significant result.

'NA' is shown where the ATC codes selected for the analysis have been used for the first time after the last three-year period considered or when the statistical tests cannot be carried out.



Regression lines per province showing a possibly different slope for the last three years (2019-2021) compared to the years before (2011-2019).

Data of 2020 was excluded from this analysis, but is indicated on the graph for information.

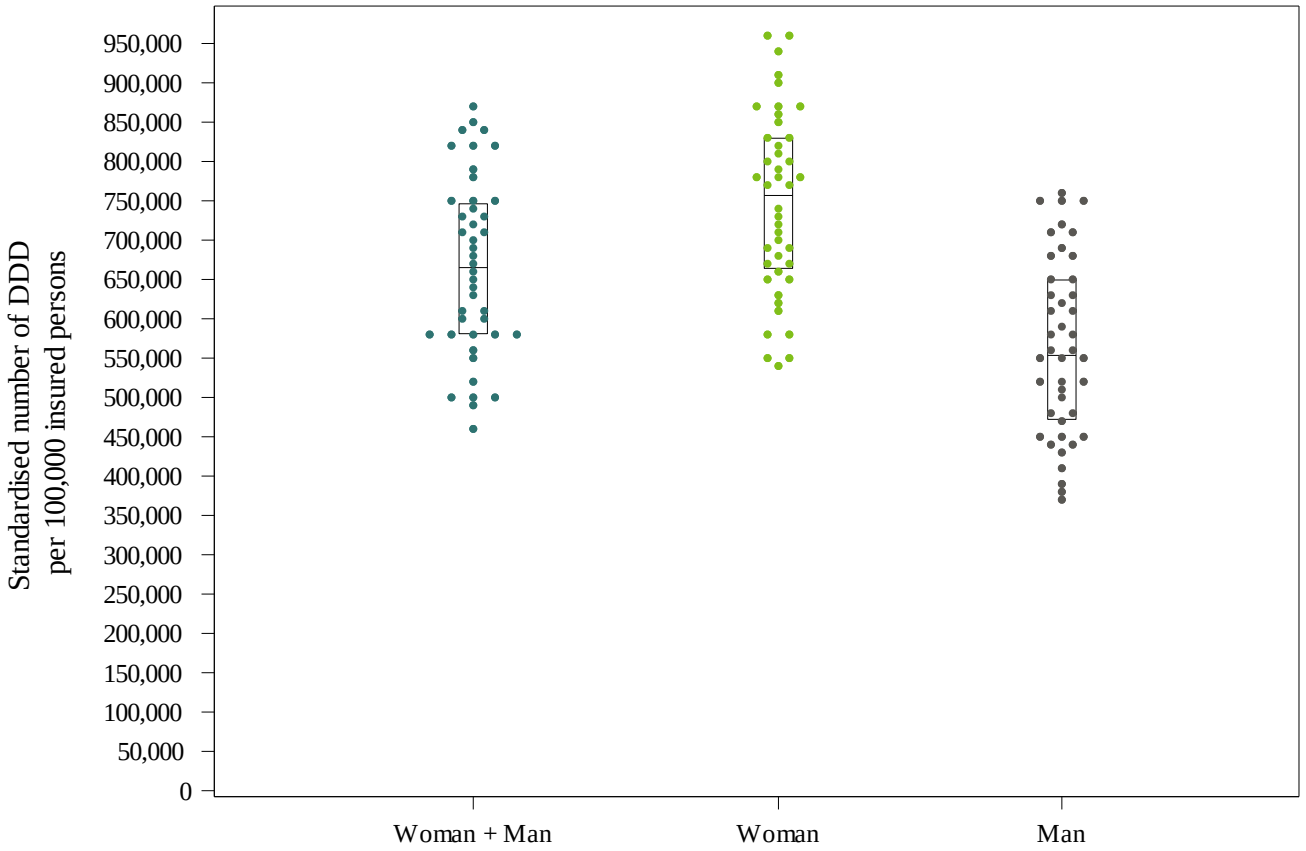
Trend break assessment model by province – Regression lines

G. Geographical variations in standardised rates of use

	TOTAL
Annual consumption (DDD)	70.049.749
Coefficient of Variation (2021)	16,85
Max/Min Ratio* of the standardised rates of use (by region)	1,58
Max/Min Ratio* of the standardised rates of use (by district)	1,88

Coefficient of Variation (2019-2021)	16,96
Coefficient of Variation (2011-2013)	24,07
Statistically significant difference? ($p \leq 0.05$)	*No*

** An 'NA' result indicates a ratio which cannot be calculated, i.e. the minimum value = zero (cf. D. Standardised rate of use by sex and age group)*

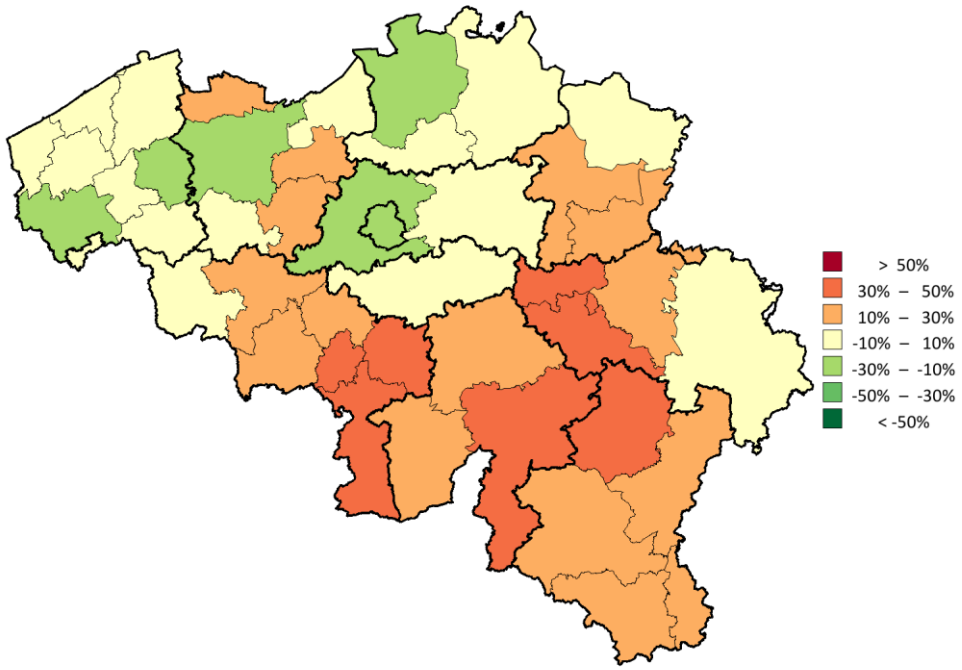


'Dot plot' showing standardised rates of use by district, by sex

A **dot plot** is a distribution chart, which is useful for highlighting groups in the data, gaps in the distribution and outliers. Here, each dot represents the rate of use of a district, for its entire population or broken down by sex.

The rates are rounded to the nearest unit, ten, hundred, etc., depending on the value of the maximum rate, in order to better group the values.

The graph also shows a box with the 25th, 50th and 75th percentiles of the non-rounded standardised rates of use for all patients. The bottom line of the box represents the 25th percentile, while the upper line represents the 75th percentile. The line inside the box represents the 50th percentile.

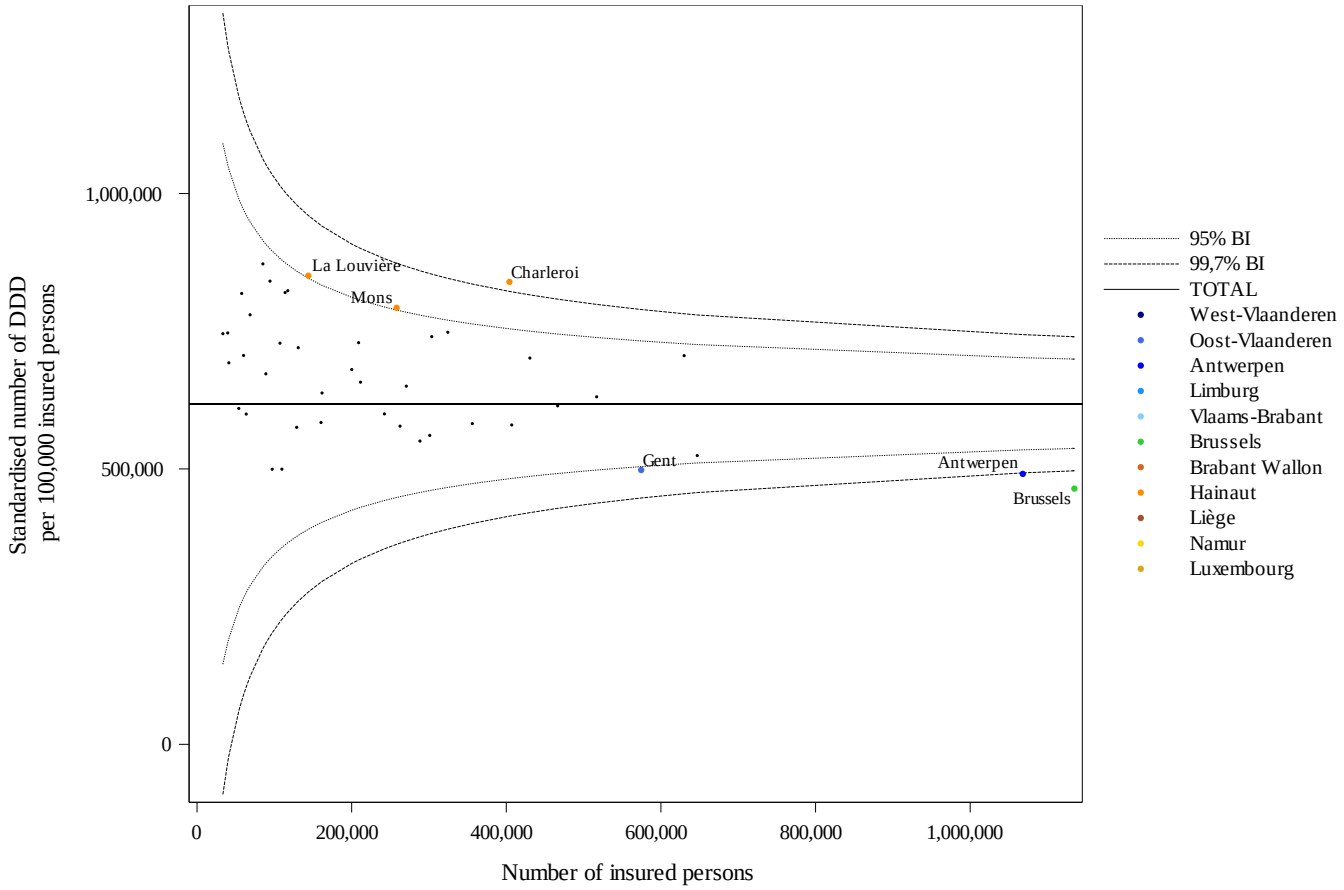


Map showing distribution of standardised rates of use, by district

On this map of Belgium, thin lines show the boundaries of the districts, while thick lines show the provincial borders. The districts are coloured using a colour scale based on the level of rate of use in the district compared to the Belgian national rate (overall rate). This ratio is expressed as a percentage: e.g. 0% if the district rate is equal to the overall rate, 20% if the rate is 20% above the overall rate, and -20% if the rate is 20% below the overall rate. The percentages are calculated using the standardised rates of the last year analysed, and are displayed in bands of 20%. The following colour coding applies:

Colour	Category
	More than 50%
	Between 30% and 50%
	Between 10% and 30%
	Between - 10% and 10%
	Between -30% and -10%
	Between -50% and - 30%
	Less than -50%
	Not used

N.B.: The interpretation of this map is to be done in parallel with the graph in funnel plot (p.23)



'Funnel plot' showing the standardised rates of use by district, by the number of insured persons

In this graph, the standardised rate of use in a district is positioned versus the size of its population. Besides the dots representing the districts, 95% and 99.7% **confidence intervals** are also shown on the graph. These are dependent of the size of the districts. The thicker horizontal line shows the national standardised rate of use. The outlier districts are identified as those districts that fall outside the 99.7% confidence intervals, the zone between the 95% and 99.7% confidence intervals being considered as "warning zone".

N.B.: The interpretation of this graph is to be done in parallel with the map of the distribution of rates of use (p.22)

H. Standardised expenditure on medicines borne by the insurance

	TOTAL
Annual consumption (DDD)	70.049.749
Annual expenditure (€)	56.235.467€
Average cost per DDD (€)	0,8€
Average annual expenditure per insured (€)	4,90€
Max/Min Ratio* of expenditure per insured (by region)	1,58
Max/Min Ratio* of expenditure per insured (by district)	1,93

** An 'NA' result indicates a ratio which cannot be calculated, i.e. the minimum value = zero (cf. D. Standardised rate of use by sex and age group)*

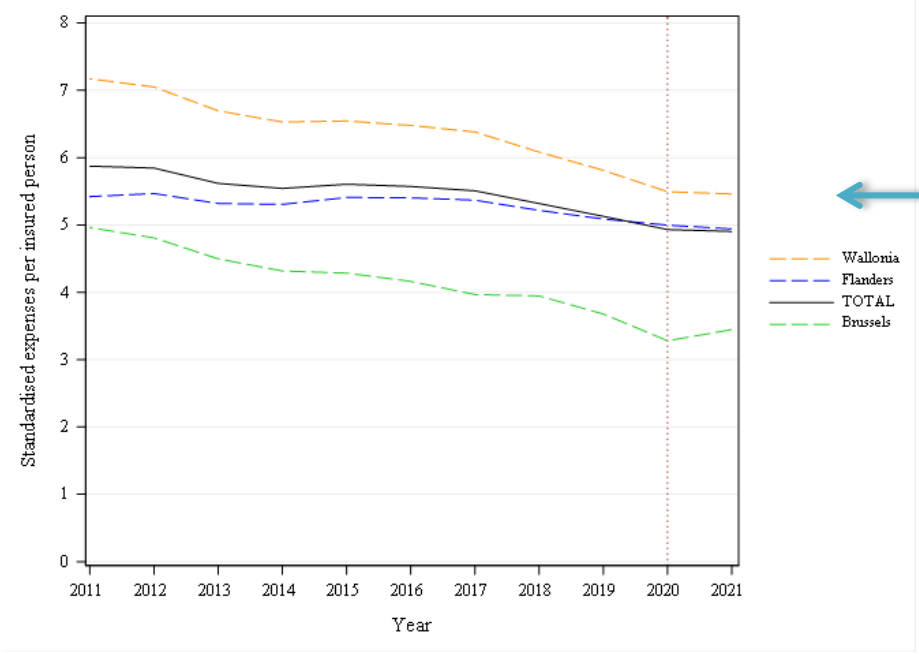
		Standardised expenditure (per insured)
Provinces	West Flanders	5,16
	East Flanders	5,09
	Antwerp	4,55
	Limburg	5,50
	Flemish Brabant	4,78
	Brussels	3,45
	Walloon Brabant	4,48
	Hainaut	5,70
	Liège	5,38
	Namur	5,85
	Luxembourg	5,60
Regions	Flanders	4,94
	Brussels	3,45
	Wallonia	5,46
	TOTAL	**4,90 €**

Regional and provincial distribution of standardised expenditure (2021)

I. Evolution of standardised expenditure per insured

	TOTAL
Annual expenditure	56.235.467€
Average annual expenditure per insured	€ 4,90
Trend (2011-2021)	-1,79%
Trend (2011-2019)	-1,68%
Trend (2019-2021)	-2,21%

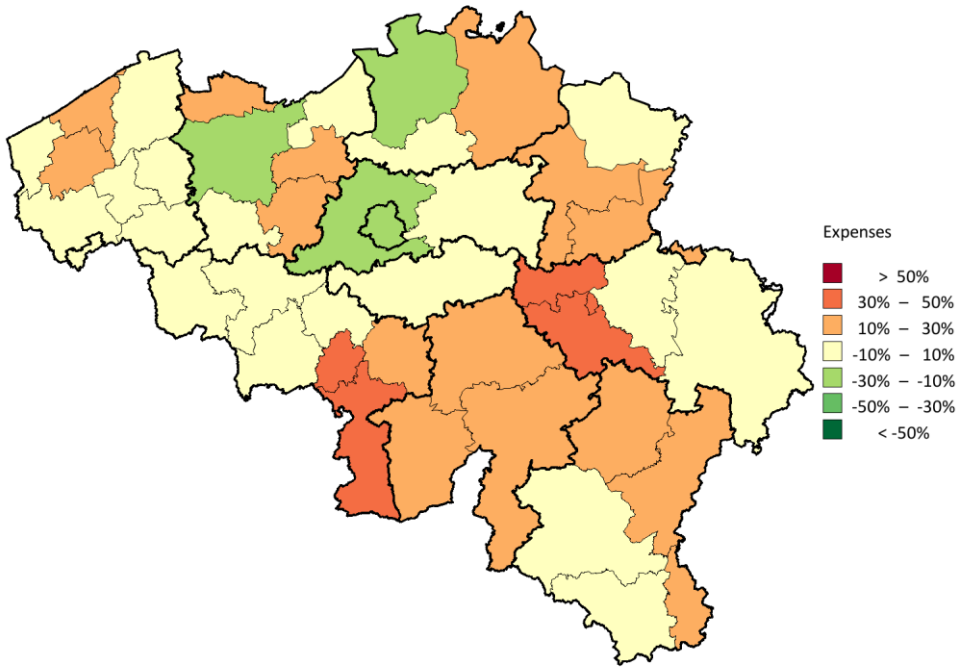
These trends correspond to the average annual growth rate.



This graph shows a coloured curve for each region and a black curve for the entire Belgian population. The x-axis shows the years, and the y-axis shows the standardised expenditure based on 2021 population data

Note : The year 2020 was highlighted by a vertical dashed line, in order to draw the attention on the impact of the COVID-19 crisis.

Evolution of standardised expenditure per insured, by region



Map showing distribution of standardised expenditure, by district

On this map of Belgium, thin lines show the boundaries of the districts, while thick lines show the provincial borders. The districts are coloured using a colour scale based on the level of expenditure in the district compared to Belgian national (overall) expenditure. This ratio is expressed as a percentage: e.g. 0% if expenditure in the district is equal to the overall expenditure, 20% if it is 20% higher, and -20% if it is 20% lower. The percentages are calculated using the standardised expenditure of the last year analysed and are displayed in bands of 20%. The following colour coding applies:

Colour	Category
	More than 50%
	Between 30% and 50%
	Between 10% and 30%
	Between - 10% and 10%
	Between -30% and -10%
	Between -50% and - 30%
	Less than -50%
	No expenditure

Code ATC	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Average annual growth rate
N02AA01	1,04	1,02	1,02	0,92	0,84	0,83	0,82	0,82	0,79	0,79	0,78	-2,83%
N02AA03	2,55	2,55	2,55	2,54	2,57	2,42	2,19	2,16	2,16	2,15	2,11	-1,88%
N02AA05	3,04	2,92	1,90	1,80	1,82	1,76	1,76	1,71	1,65	1,59	1,62	-6,09%
N02AB03	2,08	2,02	1,96	1,81	1,74	1,72	1,72	1,71	1,66	1,63	1,57	-2,76%
N02AC03	2,71	2,75	2,76	2,76	2,78	2,79	2,80	2,82	2,82	2,84	2,85	0,49%
N02AE01	1,88	1,86	1,81	1,79	1,80	1,80	1,67	1,02	1,00	0,99	0,95	-6,55%
N02AJ13	0,76	0,67	0,60	0,49	0,49	0,45	0,44	0,42	0,39	0,37	0,36	-7,12%
N02AX01	0,59	0,58	0,59	0,59	0,58	0,57	0,57	0,57	0,57	0,54	0,53	-1,05%
N02AX02	0,76	0,74	0,73	0,73	0,71	0,70	0,71	0,71	0,69	0,68	0,68	-1,15%
N02AX06	0,00	0,00	0,00	0,00	0,00	0,00	0,00	4,36	4,39	4,40	4,42	0,48%

Evolution of expenditure per DDD and per ATC code

J. Expenditure on medication charged to the patient (patient share)

	TOTAL
Annual consumption (DDD)	70.049.749
Annual expenditure (€)	56.235.467 €
Total share of patients	15.989.713 €
Average annual share per patient (€)[4]	14,5 €
% charged to the patient [5]	22,14%

** An 'NA' result indicates a ratio which cannot be calculated, i.e. the minimum value = zero (cf. D. Standardised rate of use by sex and age group)*

[4] The average financial contribution paid per year per patient consuming the medicine is calculated by dividing the total contribution by the number of patients consuming the medicine.

[5] This is the patient's share of the annual expenditure plus the patient's share of the cost of medicines supplied under the insurance scheme.

4. KEY DATA SUMMARY

RATE OF USE		
Main prescribers: ***General medicine***	**85%**	
Annual consumption (DDD)	**70.049.749**	
Standardised rate of use (per 100 000 insured persons)	**610.978**	
Average annual consumption per patient (DDD)[6]	**63**	
% Insured concerned	**9,64%**	
Approximate %DDD issued other than NIHDI[7]	**20,3%**	
% Patients with more than 3 times the average consumption[8]	**8,6%**	
POPULATION		
Median age	**63** years	
Max/min ratio[9] **of the median age** (by district)	**1,12**	
Percentage of women	**62,0%**	
Ratio Preferential rate/General rate	**2,88**	
TRENDS (DDD)		
Trend (2011-2021)	**1,14%**	
Trend[10] (2011-2019)	**1,63%**	***
Trend[10] (2019-2021)	**-0,78%**	
GEOGRAPHICAL VARIATIONS		
Coefficient of variation[10] (2011-2013)	**24,07**	NS
Coefficient of variation[10] (2019-2021)	**16,96**	
Max/min ratio of consumption (DDD)[9] (per 100 000 insured persons, by district)	**1,88**	
DIRECT EXPENDITURE		
Average annual expenditure	**56.235.467€**	
Average annual expenditure per insured	**4,90** €	
Average patient share	**22,14 %**	
Max/Min Ratio of expenditure per insured[9] (by district)	**1,93**	
% Low-cost medication	**87,19%**	
Trend (2011-2021)	**-1,79%**	
Trend (2019-2021)	**-2,21%**	
VARIATIONS IN TERMS OF MOLECULES DELIVERED		
Variations between molecules delivered[11] (by province)	**Yes**	***

[6] This is the total number of DDD dispensed divided by the number of patients who received the drug. More detailed results are shown in a document enclosed to this report.

[7] This is the difference between the declarations of sales by wholesalers to pharmacies (IQVIA database) and what is paid by the NIHDI converted into DDD and related to the total declarations of sales to public pharmacies by wholesalers. This is a contextual indicator with an approximate value.

[8] More detailed results are shown in a document enclosed to this report.

[9] An 'NA' result indicates a ratio, which cannot be calculated, i.e. the minimum value equals zero.

[10] Si If the result(s) show(s) a significant difference, the level of statistical significance is symbolized by one to three asterisks (increasingly significant). Otherwise, NS is displayed (not significant). 'NA' indicates the test is not applicable.

[11] This is the difference between the declarations of the public pharmacies (DB IQVIA) and what is invoiced within the context of the NIHDI, converted into DDD and related to the total declarations of sales in public pharmacies.

5. APPENDICES

A. Analysis of variance (ANOVA), except Brussels

Statistical significance of the differences observed in 2021		
By region?	Yes	***
By sex?	Yes	***
By reimbursement scheme?	Yes	***
By sex and per region?	No	NS
By reimbursement scheme and per region?	No	NS
By sex and per reimbursement scheme?	Yes	**
By sex and reimbursement scheme and per region?	No	NS

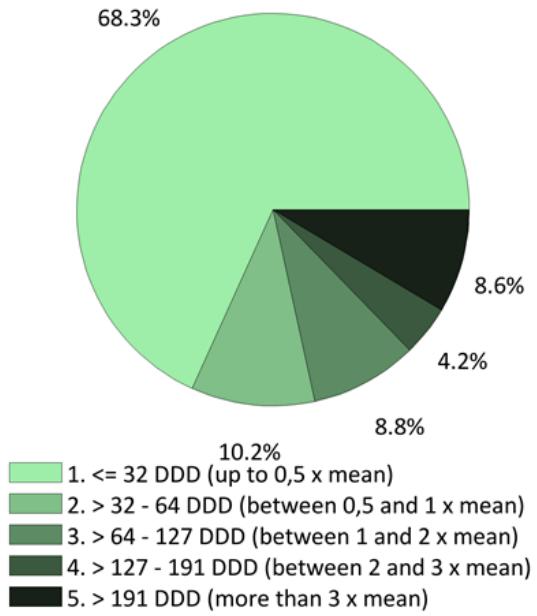
In order to be able to assess the significance of the observed differences, a linear mixed ANOVA model was fitted to the data of all districts of the Walloon and Flemish regions, after standardising for age. The model has region, sex and reimbursement scheme as fixed effects and also contains all two-way and three-way interactions between these effects.

In order to interpret the model correctly, first the three-way interaction should be evaluated, followed by the two-way interactions and finally by the main effects. If the three-way interaction is significant, the interpretation of the model should be done at this level only and the two-way interactions and main effects should not be interpreted. If the three-way interaction is not significant, the two-way interactions are evaluated. Every main effects that appears in a significant interaction should be interpreted at the level of the interaction and not at the level of that main effect. Main effects can only be interpreted directly if they don't appear in a significant interaction.

The **asterisks** represent the level of statistical significance of the tests: * P-value ≤ 0,05 / ** P-value ≤ 0,01 / *** P-value ≤ 0,001 or NS for a non-significant result.

B. Distribution of patients according to the annual dose delivered

Frequency	Per year
≤ to ½ average annual consumption	68%
>0,5 and ≤1 times the average annual consumption	10%
>1 and ≤2 times the average consumption	9%
>2 and ≤ 3 times the average consumption	4%
>3 times the average annual consumption	9%



Distribution of patients by annual delivered dose

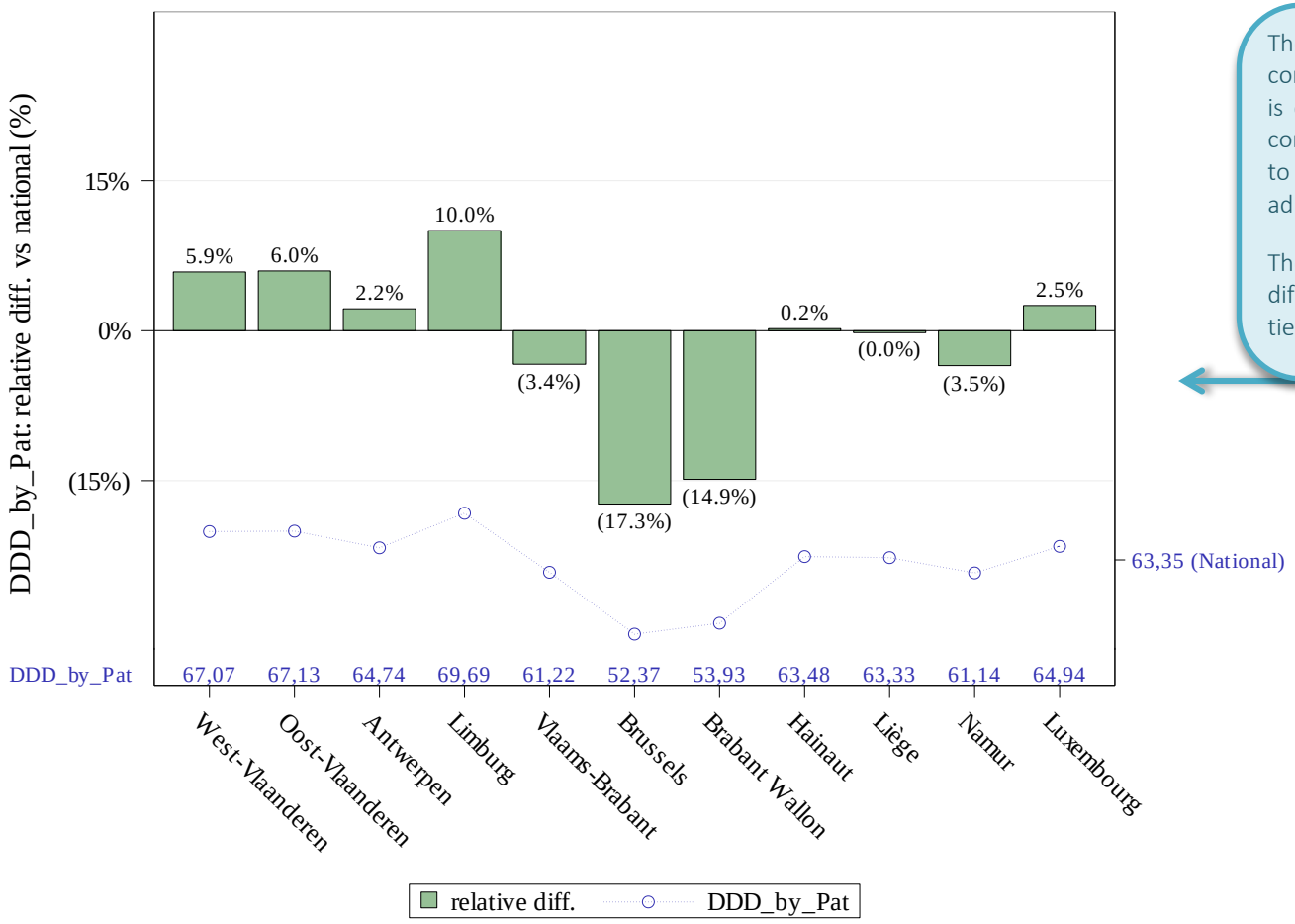
Patients (insured persons to whom the pharmacist has dispensed the medication) are divided according to the total dose dispensed annually compared to the total average annual dose.

Interpretation may vary between acute and chronic treatments.

There are several reasons why treatment may be too short:

- Doses suitable for children
- Trial treatment
- General condition of the patient (renal failure, etc.)
- Compliance
- A reduced number of episodes compared to the average (acute treatment)
- Duration of treatment may vary depending on the drug (e.g. urinary tract infection versus respiratory infection).

Reasons are reversed for higher than average durations (e.g. number of episodes of illness). But also when the prescription is renewed without taking into account the stock that the patient has at his disposal.



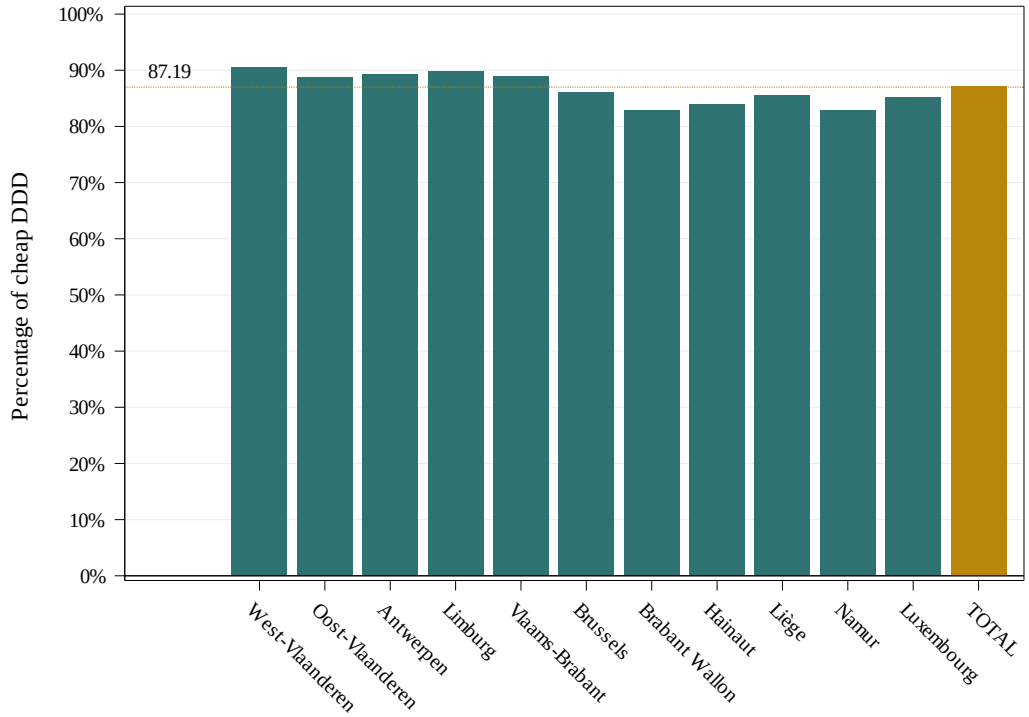
The dotted line shows the average DDD consumption per patient. The indicator is calculated by dividing the total DDD consumption by the number of insured to whom the drugs selected have been administered in the year.

The histograms by province show the difference in DDD consumption per patient compared to the national average.

Consumption per patient (DDD) by province and variation vs average national value

C. Standardised rate of use of low-cost medication

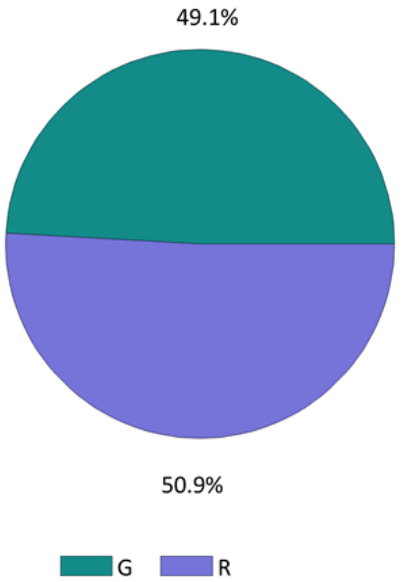
	TOTAL
Annual consumption (DDD)	70.049.749
Percentage of low-cost medication	87,19%
Max/min ratio of low-cost drug percentages (by district)	1,16



This graph shows the percentage of low-cost DDD vs the total number of DDD delivered. Besides one bar per region, an additional bar is displayed for the Belgian population. The dotted line also depicts this total ratio.

Percentage of low-cost medication delivered, in total and by province

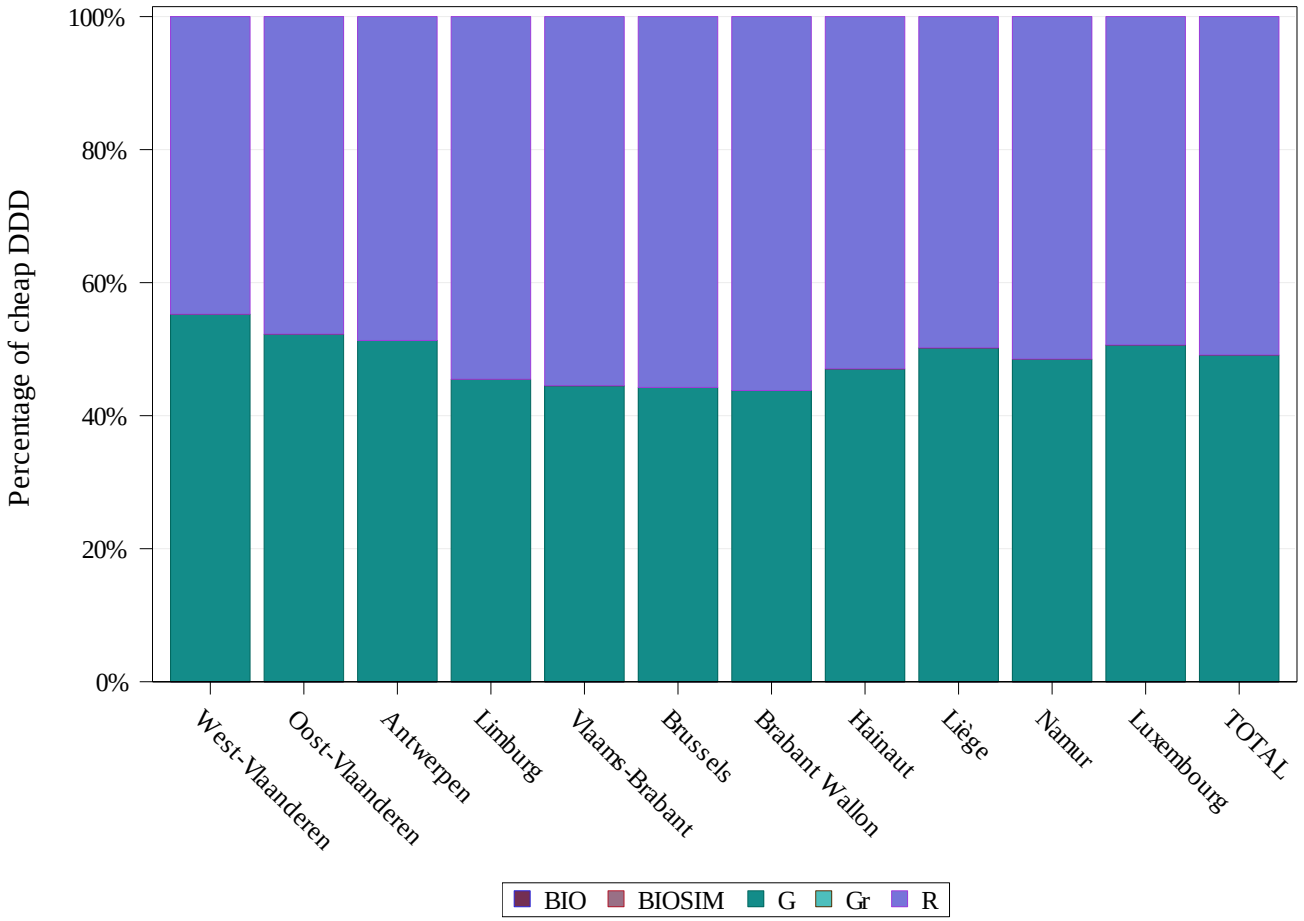
D. Percentage of low-cost medication by category



Distribution of DDD by low-cost drug class

Percentage of low-cost medication	
G	*49,1%*
R	*50,9%*

The percentage of low-cost medication is calculated per CNK code (The CNK code is a unique identification number per package, assigned to all drugs and parapharmaceuticals (medical devices, food supplements, cosmetics ...) delivered in pharmacies.
The "low-cost" status is given based on the situation in August 2022.
The letter G refers to (low-cost) generic medicines, while Gr stands for (low-cost) reference generic medicines, R = reference drugs (with the exclusion of the cheaper ones), BIOSIM stands for biosimilar medicines and BIO for biological medicines,

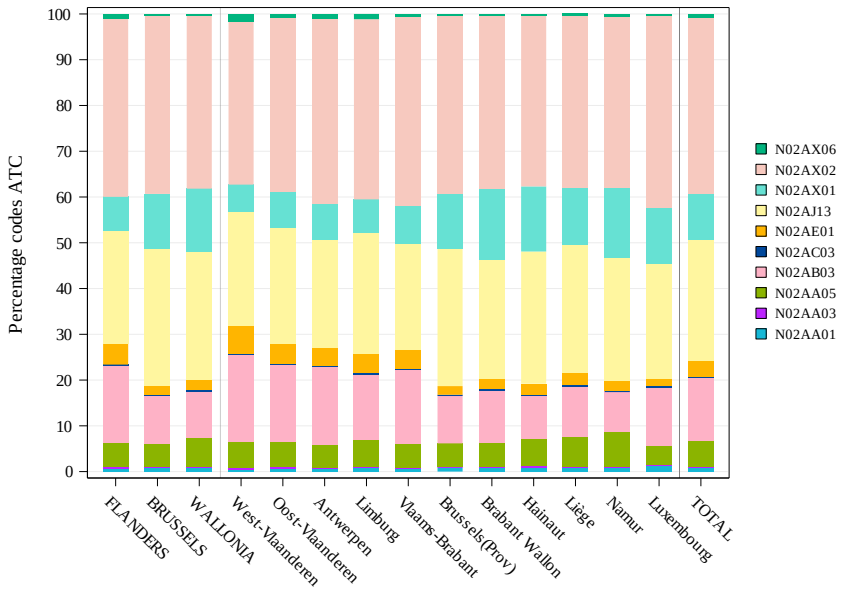


Type of low-cost drug (DDD) by province (2019)

G and Gr: low-cost generic (r= reference),
R: reference medicine not classified as low-cost,
BIO(SIM) stands for biological and biosimilar drugs.

E. Variations in medicines delivered per ATC code

➔ **Variations in prescription :**



Volume breakdown of nomenclature codes

Code_atc	Atc_FR
N02AA01	MORPHINE
N02AA03	HYDROMORPHONE
N02AA05	OXYCODONE
N02AB03	FENTANYL
N02AC03	PIRITRAMIDE
N02AE01	BUPRENORPHINE
N02AJ13	TRAMADOL ET PARACETAMOL
N02AX01	TILIDINE
N02AX02	TRAMADOL
N02AX06	TAPENTADOL

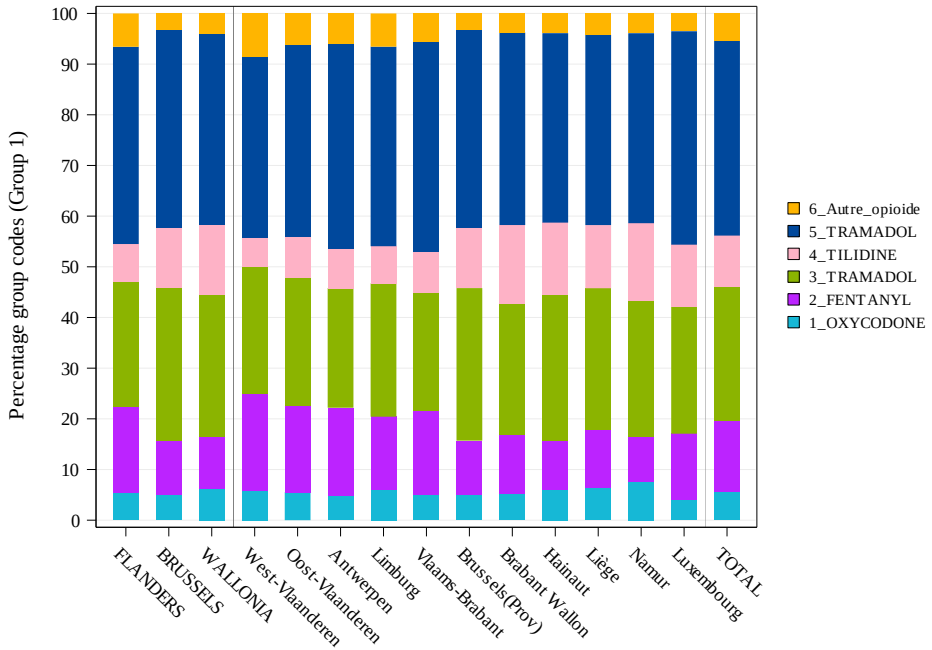
Significance	By region	By province
Use of **ATC codes**[12]	***	***

[12] The calculation of significance is carried out here by comparing the geographical differences in the use of the different nomenclature codes to code the practice.

The **asterisks** represent the level of statistical significance of Chi-square test: * P-value ≤ 0,05 / ** P-value ≤ 0,01 / *** P-value ≤ 0,001. **NS** and **NA** respectively indicate that the variations are not significant or not applicable.

F. Variations in medicines per drug group

➔ **Variations in prescription :**



Distribution of ATC codes in DDD

Significance	By region	By province
Use of **ATC codes**[13]	***	***

The **asterisks** represent the level of statistical significance of Chi-square test: * P-value ≤ 0,05 / ** P-value ≤ 0,01 / *** P-value ≤ 0,001. **NS** and **NA** respectively indicate that the variations are not significant or not applicable.

[13] The calculation of significance is carried out here by comparing the geographical differences in the use of the different nomenclature codes to code the practice.

G. Consumption sold outside the insurance

	2020
Annual consumption NIHDI (DDD)	*67.759.576*
Annual consumption outside insurance (DDD)	17.205.751
% Annual consumption outside insurance	20,3 %

ATC	fr	Volume total (IQVIA + rajout)	Volume remboursé (pharmanet)	% hors assurance
N02AA	ALCALOIDES NATURELS DE L'OPIUM	6.091.947	4.511.607	26%
N02AB	DERIVES DE LA PHENYLPIPERIDINE	10.135.248	10.025.228	1%
N02AC	DERIVES DE LA DIPHENYLPROPYLAMINE	43.798	43.798	0%
N02AE	DERIVES DE L'ORIPAVINE	2.696.439	2.682.559	1%
N02AJ	OPIOIDES AVEC DES ANALGESIQUES NON-OPIOIDES	30.417.647	17.604.096	42%
N02AX	AUTRES OPIOIDES	35.580.248	32.892.289	8%
N02A	**OPIACES**	**84.965.327**	**67.759.576**	**20,3%**

Share sold outside NIHDI per ATC group