Trends in incidence, prevalence and approach of radiating low back pain: a registry-based study with Flemish primary care data

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Abstract

Background Global data suggest that low back pain (LBP) is becoming more frequent, and most people deal with it at least once in their lives. Specific and recent data on the epidemiology of LBP with irradiation are lacking; older data suggest that out of five LBP patients, only one suffers from irradiation. Therefore, we aim to examine trends in incidence and prevalence of LBP with irradiation specifically, including comorbidity and pharmacological treatment.

Methods In this retrospective registry-based study, spanning from January 1st, 2001, until December 31st, 2020, we analysed data from 548 684 unique patients. The data are contained in the Intego database, that gets its input from 454 Flemish GPs, spread among 86 surgeries. Age-standardised incidence and prevalence were calculated for each studied year and for both sexes. A joinpoint regression analysis was then used to compute the annual percentage change (APC) and average annual percentage change (AAPC) from both those variables, as well as for medication use. To evaluate the trends in comorbidity, we used the Jonckheere-Terpstra and Cochran-Armitage tests.

Results While the total age-standardised prevalence of LBP with irradiation increased significantly from 2001 to 2020, i.e., from 9.46 to 13.25 cases per 1 000 patients, the incidence did not. The number of LBP patients with irradiation patients suffering from the four most frequent comorbid diagnoses, i.e., hypertension, asthma, irritable bowel syndrome (IBS), and osteoarthritis (OA), increased significantly in the same period, except for OA; their respective 2020 percentages being 24.3%, 13.3%, 11.3% and 18.7%. The consumption of paracetamol, benzodiazepines, anti-epileptics, antidepressants, and opioids increased significantly, that of non-steroidal anti-inflammatory drugs (NSAIDs) did not.

Conclusion The rising prevalence of LBP with irradiation confirms the known global trend for LBP in general. The increasing comorbid burden and number of prescriptions should be a cause for concern and addressed as per the new evidence-based guidelines.

Nederlandstalig abstract

Achtergrond Gegevens op mondiaal niveau suggereren dat lage rugpijn (LBP) frequenter wordt; de meeste mensen hebben er tijdens hun leven minstens éénmaal mee te maken. Op heden zijn er echter geen recente epidemiologische gegevens over LBP met uitstraling in het bijzonder. Wij wensen dus de trends in incidentie en prevalentie van LBP met uitstraling, inclusief comorbiditeit en medicamenteuze behandeling, te onderzoeken.

Methoden In deze retrospectieve databankstudie, die liep van 1 januari 2001 tot en met 31 december 2020, analyseerden wij de gegevens van 548 684 unieke patiënten van wie de gegevens opgenomen zijn in de Intego-databank. Deze gegevens zijn afkomstig van 454 Vlaamse huisartsen uit 86 praktijken. De incidentie en prevalentie, gestandaardiseerd naar leeftijd, werden voor elk bestudeerd jaar berekend, en dit per geslacht. Vervolgens deden we een joinpoint regressieanalyse om het jaarlijkse veranderingspercentage (APC) en het gemiddelde jaarlijkse veranderingspercentage (AAPC) te berekenen, wat we ook deden voor het medicatiegebruik. Voor de beoordeling van de trends in comorbiditeit, gebruikten we de Jonckheere-Terpstra- en Cochran-Armitage-tests.

Resultaten Terwijl de totale prevalentie van LBP met uitstraling, gestandaardiseerd naar leeftijd, significant toenam van 2001 tot 2020, namelijk van 9,46 naar 13,25 gevallen per 1 000 mensen, bleef de incidentie stabiel. Het aantal patiënten met LBP met uitstraling met één van de vier meest frequente comorbiditeiten, namelijk hypertensie, astma, irriteerbare darmsyndroom (IBS) en artrose, nam ook significant toe, behalve in het geval van artrose. De respectievelijke percentages voor 2020 bedroegen 24,3%, 13,3%, 11,3% en 18,7%. Het gebruik van paracetamol, benzodiazepines, anti-epileptica, antidepressiva en opioïden steeg significant, dat van niet-steroïdale antiflogistica (NSAID's) niet.

Besluit De stijgende prevalentie van LBP met uitstraling bevestigt de gekende, mondiale trend voor LBP in het algemeen. De toename van de comorbide ziektelast en van het aantal medicatievoorschriften is verontrustend en zou aangepakt moeten worden volgens de actuele evidence based richtlijnen.

Introduction

Low back pain (LBP) is an important global health concern; it is the leading cause of *years lived with disability* (YLD) (1,2). In 2010 and 2019, it was the sixth most important cause of number of *disability adjusted life years* (DALY), whereas it was only the eleventh in 1993 (2–4). In total, 60 to 90 percent of humans suffer from it at least once in their lifetime (5). These global data suggest that LBP is on the rise. The prevalence of acute and chronic LBP is increasing over time in the United States of America, a trend partially secondary to the higher prevalence in older patients and the ageing of the population (6). Also potentially tributing to this phenomenon might be an increased medicalisation of LBP (7). Data from the Belgian population are lacking.

Multiple findings indicate that LBP with irradiation, specifically, is a clinically and epidemiologically distinct entity from LBP without irradiation: different risk factors, a younger age at onset, a more axial location of pain, more intense pain and a less favourable prognosis (8–12). Most papers, though, focus on LBP without irradiation, and literature focused on LBP with irradiation is generally outdated or imprecise because of varying definitions: one 1999 paper estimates that only 2% of LBP patients suffer from irradiation; although using 1994 data, 19% of LBP patients would have had irradiation (13–15).

In 2017, the Belgian Health Care Knowledge Centre (KCE) devised a guideline and a clinical pathway in order to streamline and uniformize the approach of LBP with and without irradiation (16). Because its clinical approach is rather dissipated (patients consult general practitioners (GPs), Accident & Emergency wards and specialist consultations), the quality of care is suspected to be inconsistent and the burden to patients and society cannot be neglected. One of the goals of the pathway is to avoid chronic LBP (i.e., LBP lasting over three months), a condition that is associated with a significantly higher prevalence of depression, anxiety and sleep disorders; moreover, those patients consume significantly more opioids and benzodiazepines (17–20). For LBP with irradiation and for acute LBP, no such data are available. However, in theory, the therapeutical approach consists essentially of self-management, exercise, and physical therapy; pharmacological interventions are only warranted if this primary strategy fails. The first agent of choice is a non-steroidal anti-inflammatory drug (NSAID) (21).

The annual economic cost of chronic LBP to Belgian society is thought to be 270 to 1600 million euros in a 2006 KCE report, that is 1.4% to 8.6% of the total Belgian health budget (22,23). More recent, Dutch numbers indicate that total annual costs for a chronic LBP patient with irradiation add up to 18,940.58 euros, of which almost four fifths are societal costs, as opposed to little over 20% are strictly medical costs (8).

Putting aside the economic consequences of (chronic) LBP, the impact of this disease on the individual patient is substantial. An important decline in physical and psychological health is perceived, and participation in society is compromised: functioning as member of the workforce or as family member is rendered arduous. Thus, the consequences of LBP reach further than solely the spine (6,24,25).

Therefore, in the present paper, we chiefly aim to examine trends in incidence and prevalence of LBP with irradiation from 2001 to 2020. The second research question is to estimate the presence of comorbidity in our Flemish dataset and its evolution over time. Thirdly, and lastly, we intend to describe prescription habits and their changes as a function of time for patients suffering from sciatica.

Methods

Data collection

Data were obtained from Intego, a general practice-based computerized morbidity registration network covering Flanders, the northern region of Belgium. Intego contains longitudinal information on 253 539 patients, corresponding to 3.8 % of the Flemish population and is representative for the population in terms of age, sex and mean taxable income. Information is routinely collected in the electronic health records from 454 GPs during daily practice (2019 numbers). GPs register patient information, new diagnoses, laboratory results and new drug prescriptions. They use keywords in a predetermined field in the electronic health record. Each of the keywords is associated with a program specific internal code and can be linked to the International Classification of Primary Care (ICPC-2) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Drugs are classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system. The denominator was the yearly contact group (YCG). These are the patients that visited the practice at least once in a given year. Participation in Intego requires GPs to pass quality criteria. The average number of new diagnoses per patient per year should be higher than one, the percentage of diagnoses recorded without using key words should be less than five percent and these parameters must be stable for three years. External validation of the Intego database has been examined by means of national and international comparisons (26–29). In our study, we use data entered in the electronic health records from 01.01.2001 to 31.12.2020 (both dates included). Patients were divided into discrete age categories: age < 20, 20 ≤ age < 45, 45 ≤ age < 65, 65 ≤ age.

Definition of low back pain with irradiation

In ICPC-2, low back pain with irradiation is coded as L86 and requires an intervertebral disc prolapse or degeneration, or the clinical syndrome of sciatica (27). All existing and new diagnoses coded as L86 were effectively considered to be a case of LBP with irradiation, with no regard for the precise cause. As internal Intego guidelines (see Supplement I) dictate that an L86 episode lasts one year, a new episode is counted if no new coded L86 diagnosis is made within the rolling year after the coding of the initial L86 diagnosis. Therefore, the same patient can be counted multiple times.

Comorbid illnesses

Based on pre-existent literature on the epidemiology of LBP with or without irradiation, and its comorbidity, we looked for a precise selection of comorbid illnesses (the exhaustive list can be found in Supplement II). All diseases in this list were registered on the double condition that the comorbid episode started before the L86 episode and that the timespan between the beginning of the comorbid episode and the beginning of the L86 episode was not greater than the registration free interval for that comorbid diagnosis (see Supplement I). The second condition was installed to avoid finding irrelevant correlations.

Pharmacological treatment

Medication use was extracted from the Intego database using the corresponding ATC codes for medication frequently used in the treatment for LBP with or without irradiation for prevalent cases (as opposed to the extraction for comorbidity) during the calendar year(s) in which the LBP episode was active. A precise list is printed in Supplement III.

Data analysis

As per other studies using Intego data (30), we executed a joinpoint regression analysis. A joinpoint is a moment in time where a statistical trend is significantly changed; the analysis calculates how many joinpoints there are and at what exact moment they present themselves (31). The software tests different hypotheses, going from

zero to y joinpoints, and attempts to find the hypothesis that best fits reality. From the joinpoint regression model, one can deduct annual percentage change (APC) and average annual percentage change (AAPC) in incidence and prevalence of LBP with irradiation. The APC is a measure for the increase or decrease of the sciatica rates over the course of a year, where it is assumed they change at a constant percentage of the rate of the previous year – it is only calculated with data from within two joinpoints (32). The AAPC, however, is a summary measure of the trend over a pre-specified fixed interval. It allows us to use a single number to describe the average APCs over a period of multiple years. It is valid even if the joinpoint model indicates that there were changes in trends during those years. It is computed as a weighted average of the APCs from the joinpoint model, with the weights equal to the length of the APC interval (33).

To evaluate the trends in comorbidity of sciatica, the Jonckheere-Terpstra and Cochran-Armitage tests were deployed in fixed time intervals. Prescription behaviour was analysed using the joinpoint regression model as indicated above. Results were considered significant on the condition that $P < 0.05$.

The following software was used: SEER*Stat (available for download at https://surveillance.cancer.gov/joinpoint/) and R Software V.3.3.2 (Free Software Foundation, Boston, Massachusetts, USA) (DescTools and clinfun packages).

The Intego procedures were approved by the ethical review board of the KU Leuven Faculty of Medicine (no. ML 1723) and by the Belgian Privacy Commission (no. SCSZG/13/079) (30).

Results

Trends in age standardised incidence and prevalence of LBP with irradiation (2001 – 2020)

The Intego database contained 548 684 unique patients during the designated time window, ranging from January 1st 2001 to December 31st 2020. The age-standardised incidence of LBP in the total population only changed significantly between 2013 and 2020, where the APC was 4.4 (95% CI 1.4 to 7.5). The rates from 2001 and from 2020 did not differ significantly; their respective values were 11.02 and 11.49 new cases per 1000 patients per year. Only relatively small differences existed between women and men. The prevalence, on the other hand, increased significantly from 2001 to 2020; this change was observed in the total population (AAPC 2.0 (95% CI 0.8 to 3.1)) as well as in women (AAPC 1.5 (95% CI 0.4 to 2.7)) and men (AAPC 1.3 (95% CI 0.4 to 2.1)) separately. Shorter timespans within the total study window showed a combination of significant and non-significant changes in prevalence. E.g., the prevalence for the total population decreased significantly from 2004 to 2012 (APC -1.8 (95% CI -3.0 to -0.6)), after which first a significant albeit modest increase was noted from 2012 to 2018 (APC 2.9 (95% CI 0.7 to 5.1)) and, secondly, a significant and important rise of the rate was observed from 2018 to 2020 (APC 12.3 (95% CI 6.0 to 18.9)). Therefore, a rising trend was observed for both incidence and prevalence in the second decade of the 21st century.

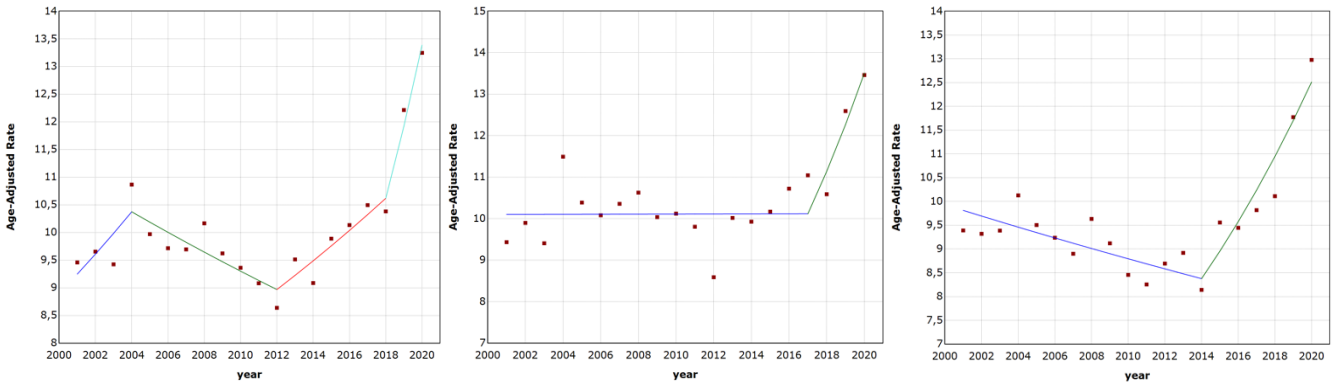
As can be seen in Table 2 and Supplement IV, there was a significant increase in the median age of patients with LBP with irradiation, i.e., from 52.3 years to 53.8 years, when comparing 2001 and 2020. The proportion of women increased significantly within the same time span, i.e., from 52.3% to 54.8%.

Table 1: ***Trends in age standardised incidence and prevalence of LBP with irradiation*** *(2001 – 2020)*

	Year 2001	**Year 2020**	**Summary AAPC (95% CI)**	**Trend 1 Years**	**Trend 1 APC (95% CI)**	**Trend 2 Years**	**Trend 2 APC (95% CI)**	**Trend 3 Years**	**Trend 3 APC (95% CI)**	**Trend 4 Years**	**Trend 4 APC (95% CI)**
Incidence of LBP with irradiation (per 1000, per year)											
Total	11.02	11.49	0.7 (-0.7 to 2.1)	2001-2013	-1.4 (-2.9 to 0.2)	2013-2020	4.4 (1.4 to 7.5)	N/A	N/A	N/A	N/A
Women	11.30	11.75	0.6 (-0.8 to 2.0)	2001-2012	-1.3 (-3.1 to 0.5)	2012-2020	3.3 (0.8 to 5.8)	N/A	N/A	N/A	N/A
Men	10.65	11.18	0.7 (-0.8 to 2.3)	2001-2013	-1.7 (-3.4 to 0.0)	2013-2020	5.1 (1.7 to 8.6)	N/A	N/A	N/A	N/A
Prevalence of LBP with irradiation (per 1000)											
Total	9.46	13.25	2.0 (0.8 to 3.1)	2001-2004	3.9 (-1.3 to 9.4)	2004-2012	-1.8 (-3.0 to -0.6)	2012-2018	2.9 (0.7 to 5.1)	2018-2020	12.3 (6.0 to 18.9)
Women	9.43	13.46	1.5 (0.4 to 2.7)	2001-2017	0.0 (-0.8 to 0.8)	2017-2020	10.1 (3.3 to 17.3)	N/A	N/A	N/A	N/A
Men	9.39	12.98	1.3 (0.4 to 2.1)	2001-2014	-1.2 (-2.1 to -0.3)	2014-2020	6.9 (4.6 to 9.3)	N/A	N/A	N/A	N/A

AAPC: average annual percentage change, CI: confidence interval, LBP: low back pain, N/A: not applicable

Figure 1: ***Age-standardised prevalence of LBP with irradiation*** *(2001 – 2020): age-standardised prevalence as a function of time with separate curves for men and women; total, women, and men, respectively.*



Incidence and prevalence of LBP with irradiation per age stratum (2001 – 2020)

The rates for incidence without age standardisation displayed a peak around 2019, where the age group with the consistently highest rates was that from 45 to 65 years (see Figure 2). In 2001, the number of new cases per 100 Intego patients and per year amounted to 0.03, 1.04, 1.89 and 1.57 for the respective age groups of age < 20, 20 ≤ age < 45, 45 ≤ age < 65 and age ≥ 65. In 2020, those numbers evolved to respectively 0.03, 1.07, 2.04 and 1.56.

The rates for prevalence, on the other hand, seemed to show a bimodal distribution with a peak in 2004 and a second one in 2020, where again the 45 to 65 years age group displayed the highest numbers (see Figure 3). In 2001, the number of prevalent cases per 100 Intego patients and per year amounted to 0.03, 0.81, 1.67 and 1.43 for the respective age groups of age < 20, 20 ≤ age < 45, 45 ≤ age < 65 and age ≥ 65. In 2020, those numbers evolved to respectively 0.02, 1.13, 2.41 and 1.96.

Figure 2: ***Incidence of LBP with irradiation*** *(2001 – 2020): incidence as a function of time with separate curves for each distinct age category, per 100 patients in the Intego database and per year.*

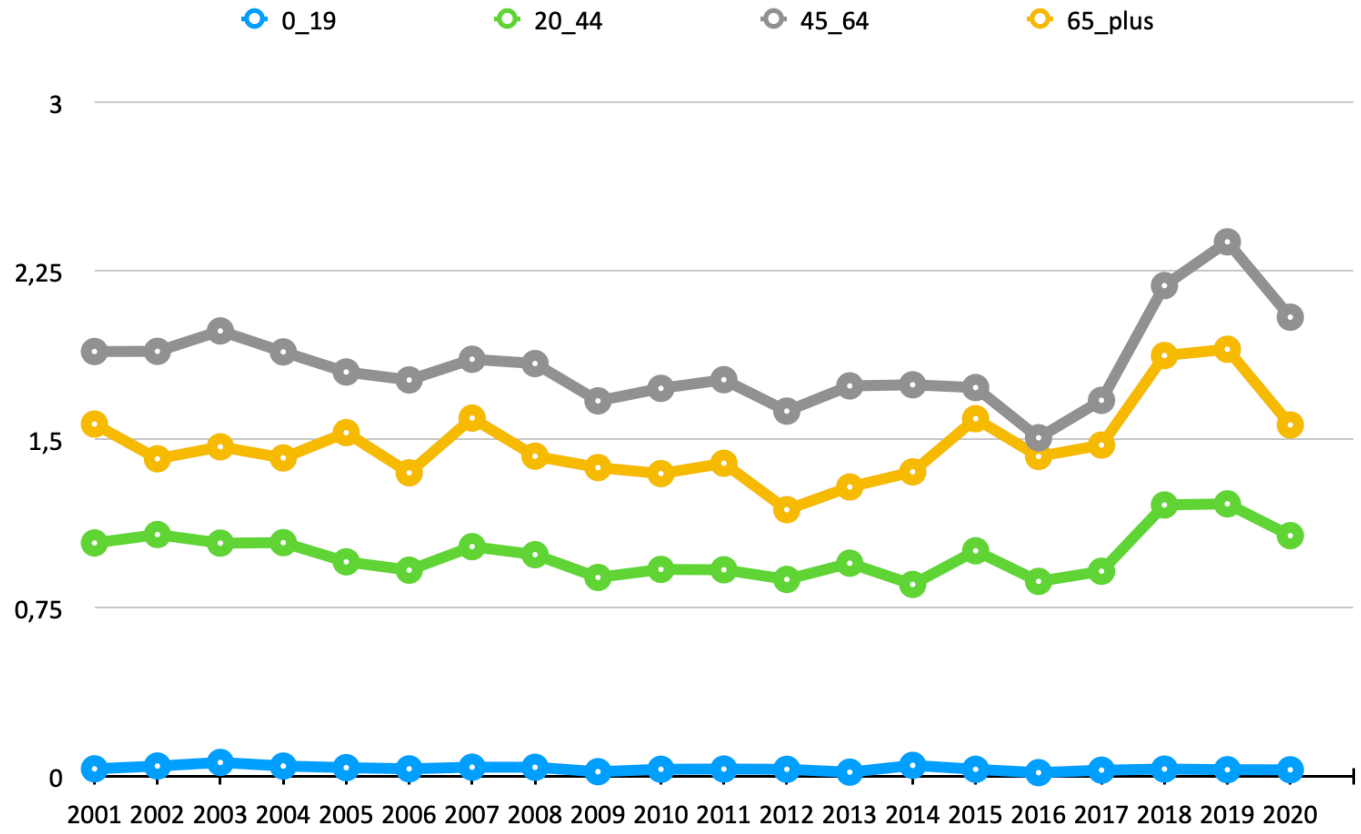
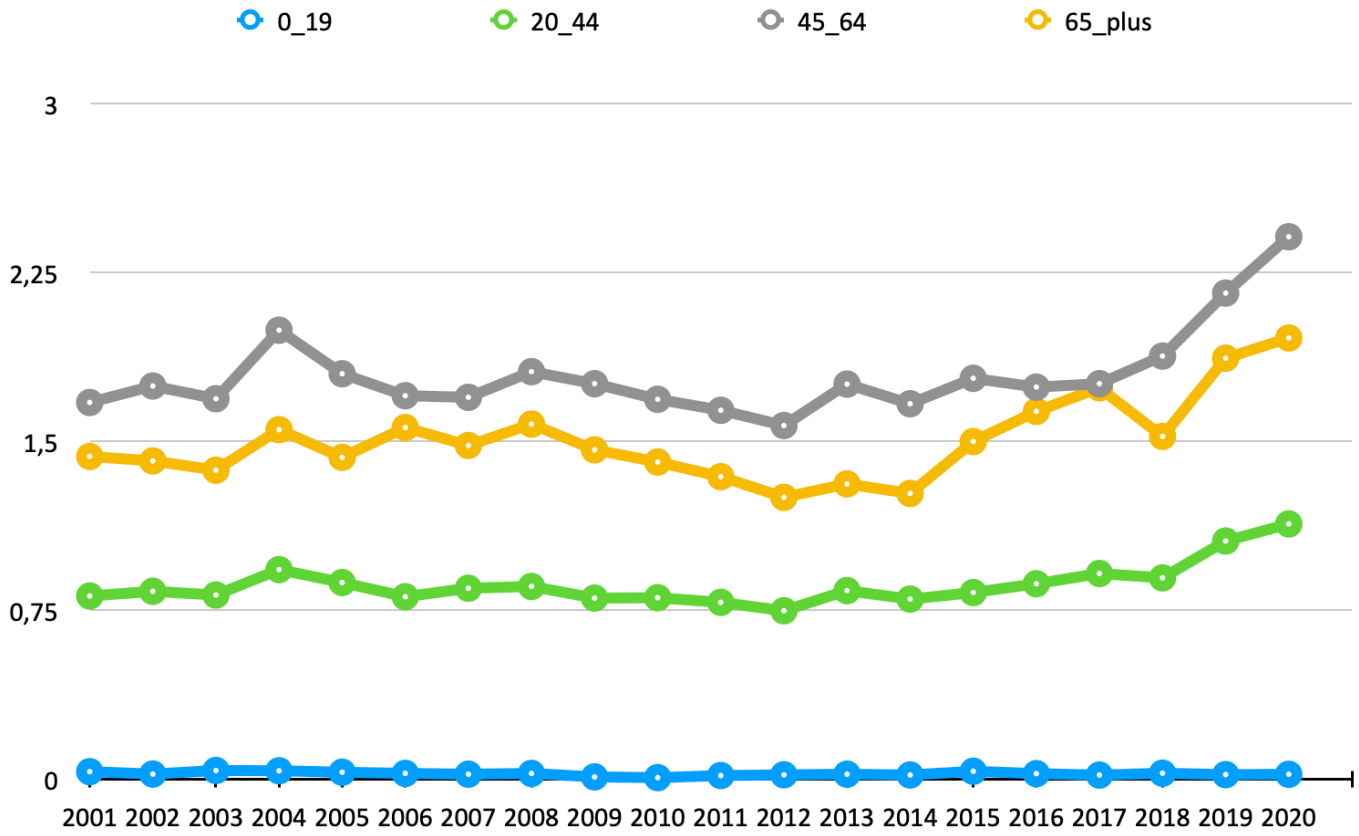


Figure 3: ***Prevalence of LBP with irradiation*** *(2001 – 2020): prevalence as a function of time with separate curves for each distinct age category, per 100 patients in the Intego database.*



Trends in comorbidities in patients with LBP with irradiation (2001 – 2020)

From 2001 to 2008, the three most frequent comorbid diagnoses were, in decreasing numbers, hypertension, osteoarthritis (OA) and irritable bowel syndrome (IBS). Between 2009 and 2012, however, asthma became the second comorbid diagnosis, replacing OA, while IBS remained in its third place. Finally, from 2013 onwards, IBS was no longer in third place and had its place taken by OA. The final decreasing order in 2020 was therefore hypertension, asthma, and OA. For hypertension, asthma and IBS, the increasing trend was significant ($p < 0.05$).

Table 2: ***Trends in comorbidities in patients with LBP with irradiation*** *(2001 – 2020)*

Totals and illnesses	**2001-2004**	**2005-2008**	**2009-2012**	**2013-2016**	**2017-2020**	**p-value**
Patients with LBP	3683	4554	4861	4876	10132	0
Mean age (years) (2 SD)	52.3(15.9)	53.4(16.1)	53(15.9)	53.3(16.3)	53.8(16.4)	0.0004
Women n (%)	1928(52.3%)	2467(54.2%)	2635(54.2%)	2739(56.2%)	5553(54.8%)	0.0089
Irritable bowel disease	345(9.4%)	455(10%)	579(11.9%)	681(14%)	1143(11.3%)	<0.0001
Ischaemic heart disease with and without infarction	137(3.7%)	176(3.9%)	150(3.1%)	191(3.9%)	287(2.8%)	0.0033
Hypertension	651(17.7%)	897(19.7%)	1012(20.8%)	1114(22.8%)	2463(24.3%)	<0.0001
Cerebrovascular disease	76(2.1%)	101(2.2%)	116(2.4%)	136(2.8%)	345(3.4%)	<0.0001
Atherosclerosis/peripheral vascular disease	105(2.9%)	139(3.1%)	151(3.1%)	153(3.1%)	298(2.9%)	0.96
Neck symptom/complaint/syndrome	197(5.3%)	305(6.7%)	380(7.8%)	468(9.6%)	635(6.3%)	0.0891

Osteoarthritis	599(16.3%)	880(19.3%)	937(19.3%)	1089(22.3%)	1897(18.7%)	0.0056
Osteoporosis	140(3.8%)	191(4.2%)	197(4.1%)	199(4.1%)	393(3.9%)	0.7866
Asthma	302(8.2%)	432(9.5%)	582(12%)	690(14.2%)	1348(13.3%)	<0.0001
Feeling anxious/nervous/tense//anxiety disorder	17(0.5%)	31(0.7%)	23(0.5%)	26(0.5%)	146(1.4%)	<0.0001
Feeling depressed//depressive disorder	96(2.6%)	88(1.9%)	122(2.5%)	129(2.6%)	406(4%)	<0.0001
Substance abuse	103(2.8%)	144(3.2%)	186(3.8%)	301(6.2%)	769(7.6%)	<0.0001
Somatisation disorder	7(0.2%)	16(0.4%)	14(0.3%)	12(0.2%)	32(0.3%)	0.5422
Chronic obstructive pulmonary disorder	117(3.2%)	196(4.3%)	181(3.7%)	191(3.9%)	498(4.9%)	<0.0001
Obesity/overweight	9(0.2%)	31(0.7%)	19(0.4%)	40(0.8%)	157(1.5%)	<0.0001
Diabetes non-insulin dependent	193(5.2%)	305(6.7%)	411(8.5%)	608(12.5%)	999(9.9%)	<0.0001

The full list of comorbid diagnoses can be consulted in Supplement IV. For all diagnoses, we display the absolute number of patients and the ratio of this absolute number to the total number of patients within that time window as a percentage.

Trends in prescription habits for patients with LBP with irradiation (2001 – 2020)

For all medications prescribed to patients with LBP with irradiation, a rising trend could be observed, although this evolution was not significant in the case of NSAIDs. The steepest increase was noted for antiepileptics, with an AAPC of 8.0 (95% CI 6.7 to 9.4). The consumption of antidepressants and paracetamol was higher in 2020 than it was in 2001, although the general trend consisted of two separate evolutions. I.e., for antidepressants, the APC for the total population was rather modest from 2001 to 2013 and increased almost by a factor four from 2014 to 2020, the exact numbers being 1.0 (95% CI 0.2 to 1.9) and 3.7 (95% CI 2.3 to 5.2), respectively. For paracetamol, the opposite pattern was lined out, with an APC of 8.6 (95% CI 5.0 to 12.4) from 2001 to 2010 going to just 0.5 (95% CI -1.4 to 2.4) from 2011 to 2020, hence not even reaching statistical significance.

The pharmacological product that was prescribed most in 2020 for the entire population were NSAIDs (used by 42.0% of patients), the second place being occupied by opioids (24.4% of patients) and the third by antidepressants (18.6% of patients). A remarkable difference in medication use was observable between men and women, where generally more women received pharmaceutical prescriptions than men. The differences in absolute percentages in 2020 were the smallest for NSAIDs and paracetamol (3.1% and 3.0%, respectively), they were the largest for antidepressants (9.8%), in all cases in favour of women.

Table 3: ***Trends in prescription habits for patients with LBP with irradiation*** *(2001 – 2020)*

	Year 2001 (%)	**Year 2020 (%)**	**Summary AAPC (95% CI)**	**Trend 1 Years**	**Trend 1 APC (95% CI)**	**Trend 2 Years**	**Trend 2 APC (95% CI)**
Antidepressants							
Total	13.5	18.6	2.0 (1.3 to 2.7)	2001-2013	1.0 (0.2 to 1.9)	2013-2020	3.7 (2.3 to 5.2)
Women	17.3	23.0	2.0 (1.5 to 2.6)	N/A	N/A	N/A	N/A
Men	9.1	13.2	2.3 (1.5 to 3.1)	N/A	N/A	N/A	N/A
Antiepileptics							
Total	1.6	7.5	8.0 (6.7 to 9.4)	N/A	N/A	N/A	N/A
Women	2.3	9.1	8.9 (7.5 to 10.4)	N/A	N/A	N/A	N/A

Men	0.7	5.5	6.3 (4.3 to 8.4)	N/A	N/A	N/A	N/A
Benzodiazepines							
Total	17.6	18.0	1.3 (0.6 to 2.0)	N/A	N/A	N/A	N/A
Women	21.3	20.5	1.0 (0.3 to 1.7)	N/A	N/A	N/A	N/A
Men	13.4	14.9	1.5 (-1.5 to 3.5)	2001-2011	-1.4 (-4.5 to 1.7)	2011-2020	4.7 (1.8 to 7.7)
NSAIDs							
Total	43.6	42.0	0.1 (-0.2 to 0.5)	N/A	N/A	N/A	N/A
Women	45.2	43.4	-0.1 (-0.5 to 0.2)	N/A	N/A	N/A	N/A
Men	41.8	40.3	0.5 (0.0 to 0.9)	N/A	N/A	N/A	N/A
Opioids							
Total	12.0	24.4	4.0 (3.4 to 4.7)	N/A	N/A	N/A	N/A
Women	14.8	26.0	3.6 (3.0 to 4.2)	N/A	N/A	N/A	N/A
Men	8.8	22.6	4.6 (3.6 to 5.6)	N/A	N/A	N/A	N/A
Paracetamol (acetaminophen)							
Total	8.6	18.0	4.2 (2.5 to 6.1)	2001-2010	8.6 (5.0 to 12.4)	2010-2020	0.5 (-1.4 to 2.4)
Women	9.8	19.3	3.7 (2.2 to 5.2)	2001-2013	6.8 (4.8 to 8.8)	2013-2020	-1.4 (-4.0 to 1.3)
Men	7.2	16.3	3.2 (1.7 to 4.7)	N/A	N/A	N/A	N/A

AAPC: average annual percentage change, CI: confidence interval, LBP: low back pain, NSAIDs: non-steroidal anti-inflammatory drugs.

Discussion

Our retrospective registry-based study showed a statistically significant increase in the prevalence of LBP with irradiation from 2001 to 2020, although the incidence remained stable. Remarkably, the rising trend was only present from 2012 and 2013 onwards, respectively; it could not be explained by the ageing population as the rates were age-adjusted. Our findings are compatible with the existing literature (2–4) and confirm that the known, global trend at least partially applies to the Flemish population as well. Furthermore, we noticed that the rates in our dataset were significantly, though only slightly, higher in women than in men, both in 2001 and in 2020, and that the difference between them increased over time (2).

The most common comorbid diagnosis in our population was arterial hypertension; the second and third place being occupied by either OA, IBS, or asthma, in changing order over time. It is worth noting that their absolute prevalence increased, and for all but OA, this increase was statistically significant ($p < 0.05$). This last phenomenon can only be explained by advancing age of the population for hypertension and OA, which become more prevalent with increasing age, as IBS diagnoses are less prevalent in people aged 50 years and over than in younger patients (34–37). Earlier Intego research by Spitaels et al. showed that the most frequently used drugs for knee OA are NSAIDs (35), and another Intego study by Clevers et al. described an association between IBS and musculoskeletal symptoms (37). These two findings are consistent with our data. Specific attention was paid to the rates of depression, anxiety, and sleep disorders, three diagnoses that are more common in chronic than in acute LBP. In this dataset, the rates for depression fluctuated between 1.9% and 3.8%, those for anxious feelings and anxiety disorder (pooled) ranged from 0.4% to 1.5% and those for sleep disorders from 0.2% and 1.3%. Pre-existent research by Gore et al. indicated that the respective prevalence of depression and anxiety are 6.1% and 3.4% in the general population and 13.0% and 8.0% in patients with chronic LBP, in a registry-based study where chronic LBP patients were matched with controls based on sex, age and region (17). Our patients with acute LBP with irradiation displayed prominently lower rates of these illnesses. Hence, there did not seem to be a positive correlation between LBP with irradiation and depression and/or anxiety, quite the contrary.

Regarding medication use for LBP with irradiation, we found that the most prescribed pharmacological products in these patients were NSAIDs, which is in accordance with the current Belgian guidelines for LBP with irradiation (16); however, the data did not show for which indication a drug has been prescribed. As remarked before, the second most prevalent comorbid diagnosis in our population was OA and for knee OA in particular, NSAIDs were the most prescribed drugs as well (35). On the other hand, while the number of patients taking NSAIDs was consistently the highest, the numbers for other drugs increased over time, whereas those for NSAIDs themselves did not. The increase was highest for antiepileptics, possibly because GPs used them for their supposed efficacy against neuropathic pain. An alarming second place, after NSAIDs, was occupied by opioids and a third by antidepressants. They were taken by respectively 24.4% and 18.6% of LBP patients in 2020. The use of antidepressants could not be explained in a satisfying manner by the percentage of those patients that also suffered from depressive symptoms or depressive disorder, since this only amounted to 4% between 2017 and 2020. Antidepressants may have been prescribed for the same reason as antiepileptics, although both KCE and the British National Institute for Health and Care Excellence (NICE) advise against this practice, as their risk-benefit ratio is unfavourable (16,38). These rates should be a cause of concern for the public health administrations and might warrant an information campaign about the KCE guideline towards Flemish GPs. Finally, we noticed that a higher proportion of women received a pharmaceutical prescription than men did, even though we did not check for statistical significance, which is paralleled by the higher incidence and prevalence of LBP with irradiation in women than in men in our dataset.

Limitations of this study

This study counted numerous limitations, the foremost important being issues with insufficient power. It was not always possible to evaluate trends in comorbidity with our data set size. The second issue was statistical as well,

i.e., that some above mentioned findings were not checked for statistical significance. Other issues were related to the functioning of the Intego database and the process of data extraction itself. One clear example is that it was impossible to know whether a particular drug (e.g., an antiepileptic) was prescribed for LBP or for another illness (such as epilepsy), hence, no firm conclusions could be drawn about the precise indication. A second manifestation hereof was that we had no data about physical therapy prescriptions, requests for medical imaging, specialist referrals, or prescriptions for paid sick leave. This information would nonetheless be of value, because the annual direct costs for LBP in Belgium are estimated between 81 to 167 million euros, which include medical consultations, drugs, imaging, surgery and physical therapy (22). Furthermore, 12% of disability lasting more than 28 days in Belgium can be attributed to LBP, although this only concerned the cases evaluated by company medical officers; the indirect costs to society caused by decreased productivity may amount to twice the direct medical costs (7,22). And lastly, with regards to requests for medical imaging, it is known that the specificity of, e.g., magnetic resonance imaging (MRI) for LBP is poor, as with increasing age, a growing share of asymptomatic individuals bears signs of disc degeneration, annular fissure or disc protrusion or bulge, which are signs that are compatible with a L84 diagnosis as well (39,40).

Conclusion

This retrospective database study, representative of the Flemish population, confirms the global trend of an increase in prevalence of LBP, be it with or without irradiation; in 2020, the prevalence of LBP with irradiation amounted to 13.25 cases per 1000 patients.

The burden of comorbid illness is significantly increasing for an important number of diagnoses as well, e.g., the number of LBP with irradiation patients suffering from hypertension went from 17.7% (2001-2004) to 24.3% (2017-2020). On the other hand, the prevalence of psychiatric comorbidity associated with chronic LBP is remarkably lower in our patients with acute LBP with irradiation. E.g., for depression, those rates are respectively 13.0% and (at most) 3.8%.

The most prescribed pharmacological products of LBP with irradiation are NSAIDs, in accordance with the current evidence-based guidelines; 42.0% of LBP patients received a prescription for them. The use of all the other products, such as antidepressants or opioids, which are not recommended for the management of LBP with irradiation, displayed a concerning increase, e.g., the number of opioid prescriptions more than doubled between 2001 and 2020.

Supplement I: registration free interval

For all ICPC-2-diagnoses, the Intego researchers calculated the average duration of their episodes. When the default duration of an episode has elapsed, a new coding of the same diagnosis is considered a new episode. This time span is also called the registration free interval. We print a list of the registration free intervals of all comorbid diagnoses in Supplement I and the L84 and L86 diagnoses themselves.

ICPC-2 classification and disease designation	**Registration free interval**
A70 Tuberculosis	Sustained - 1 year
A79 Malignancy NOS	Chronic
A92 Allergy/Allergic reaction NOS	Sustained - 1 year
B72 Lymphoma	Chronic
B73 Leukaemia	Chronic
B74 Malignant neoplasm blood other	Chronic
D02 Abdominal pain epigastric	Acute - 16 weeks
D03 Heartburn	Acute - 16 weeks
D12 Constipation	Sustained - 1 year
D13 Jaundice	Acute - 8 weeks
D23 Hepatomegaly	Sustained - 1 year
D70 Gastrointestinal infection	Acute - 4 weeks
D72 Viral hepatitis	Sustained - 1 year
D73 Gastroenteritis presumed infection	Acute - 4 weeks
D74 Malignant neoplasm stomach	Chronic
D75 Malignant neoplasm colon/rectum	Chronic
D76 Malignant neoplasm pancreas	Chronic
D77 Malignant digestive neoplasm other/NOS	Chronic
D85 Duodenal ulcer	Acute - 16 weeks
D86 Peptic ulcer other	Acute - 16 weeks
D87 Stomach function disorder	Sustained - 1 year
D92 Diverticular disease	Acute - 16 weeks
D93 Irritable bowel disease	Chronic
D94 Chronic enteritis/ulcerative colitis	Chronic

D97 Liver disease NOS	Chronic
D98 Cholecystitis/cholelithiasis	Sustained - 1 year
F71 Conjunctivitis allergic	Sustained - 1 year
F74 Neoplasm of eye/adnexa	Chronic
H75 Neoplasm of ear	Chronic
K06 Prominent veins	Sustained - 1 year
K72 Neoplasm cardiovascular	Chronic
K74 Ischaemic heart disease with angor	Chronic
K75 Acute myocardial infarction	Sustained - 1 year
K77 Heart failure	Chronic
K85 Elevated blood pressure	Acute - 16 weeks
K86 Hypertension uncomplicated	Chronic
K87 Hypertension complicated	Chronic
K89 Transient cerebral ischaemia	Sustained - 1 year
K90 Stroke/cerebrovascular accident	Chronic
K91 Cerebrovascular disease	Chronic
K92 Atherosclerosis/peripheral vascular disease	Chronic
K94 Phlebitis/thrombophlebitis	Sustained - 1 year
K95 Varicose veins of leg	Sustained - 1 year
K99 Cardiovascular disease other	Acute - 8 weeks
L01 Neck symptom/complaint	Chronic
L71 Malignant neoplasm musculoskeletal	Sustained - 1 year
L83 Neck syndrome	Chronic
L84 LBP without irradiation	Chronic
L86 LBP with irradiation	Sustained – 1 year
L87 Bursitis/tendinitis/synovitis NOS	Sustained - 1 year
L88 Rheumatoid/seropositive arthritis	Acute - 8 weeks
L89 Osteoarthritis of hip	Chronic
L90 Osteoarthritis of knee	Chronic

L91 Osteoarthritis other	Chronic
L95 Osteoporosis	Chronic
N01 Headache	Chronic
N71 Meningitis/encephalitis	Acute - 8 weeks
N85 Congenital anomaly neurological	Sustained - 1 year
N89 Migraine	Chronic
P01 Feeling anxious/nervous/tense	Chronic
P03 Feeling depressed	Acute - 16 weeks
P06 Sleep disturbance	Acute - 16 weeks
P15 Chronic alcohol abuse	Acute - 16 weeks
P16 Acute alcohol abuse	Chronic
P17 Tobacco abuse	Sustained - 1 year
P18 Medication abuse	Chronic
P19 Drug abuse	Sustained - 1 year
P74 Anxiety disorder/anxiety state	Sustained - 1 year
P75 Somatisation disorder	Sustained - 1 year
P76 Depressive disorder	Sustained - 1 year
P80 Personality disorder	Sustained - 1 year
R02 Shortness of breath/dyspnoea	Chronic
R71 Whooping cough	Acute - 16 weeks
R72 Strep throat	Acute - 16 weeks
R73 Boil/abscess nose	Acute - 4 weeks
R74 Upper respiratory tract infection acute	Acute - 4 weeks
R75 Sinusitis acute/chronic	Acute - 4 weeks
R76 Tonsillitis acute	Acute - 8 weeks
R77 Laryngitis/tracheitis acute	Acute - 4 weeks
R78 Acute bronchitis/bronchiolitis	Acute - 4 weeks
R79 Chronic bronchitis	Acute - 8 weeks
R80 Influenza	Chronic

R81 Pneumonia	Acute - 4 weeks
R82 Pleurisy/pleural effusion	Acute - 16 weeks
R83 Respiratory infection other	Acute - 16 weeks
R84 Malignant neoplasm bronchus/lung	Acute - 16 weeks
R85 Malignant neoplasm respiratory other	Chronic
R95 Chronic obstructive pulmonary disorder	Chronic
R96 Asthma	Chronic
R97 Allergic rhinitis	Chronic
R98 Hyperventilation syndrome	Sustained - 1 year
S77 Malignant neoplasm of skin	Sustained - 1 year
S78 Lipoma	Chronic
S87 Dermatitis/atopic eczema	Acute - 16 weeks
S88 Dermatitis contact/allergic	Chronic
S98 Skin disease other	Chronic
T71 Malignant neoplasm thyroid	Sustained - 1 year
T72 Benign neoplasm thyroid	Chronic
T78 Thyroglossal duct/cyst	Acute - 16 weeks
T81 Goitre	Chronic
T82 Obesity	Chronic
T83 Overweight	Sustained - 1 year
T85 Hyperthyroidism/thyrotoxicosis	Sustained - 1 year
T86 Hypothyroidism/myxoedema	Sustained - 1 year
T89 Diabetes insulin resistant	Chronic
T90 Diabetes non-insulin resistant	Chronic
U70 Pyelonephritis/pyelitis	Chronic
U75 Malignant neoplasm of kidney	Acute - 8 weeks
U76 Malignant neoplasm of bladder	Chronic
U77 Malignant neoplasm urinary tract other	Chronic
U95 Urinary calculus	Chronic

W72 Malignant neoplasm related to pregnancy	Sustained - 1 year
X08 Intermenstrual bleeding	Chronic
X17 Pelvis symptom/complaint female	Sustained - 1 year
X74 Pelvic inflammatory disease	Acute - 8 weeks
X75 Malignant neoplasm cervix	Acute - 16 weeks
X76 Malignant neoplasm breast female	Chronic
X77 Malignant neoplasm genital female other	Chronic
X89 Premenstrual tension syndrome	Chronic
X99 Genital disease female other	Sustained - 1 year
Y77 Malignant neoplasm prostate	Sustained - 1 year
Y78 Malignant neoplasm male genital other	Chronic

Supplement II: comorbid diagnoses

Diseases positively associated with LBP: **depression, anxiety** (41–44); **tobacco use** in a direct way (45); tobacco use in an indirect way through **atherosclerosis** (46,47) and through proinflammatory cytokines (48); **dyspnoea, asthma, allergy, respiratory infections** (49,50); **somatisation** (42); **headache, migraine, angina pectoris, cardiovascular disease** not otherwise specified**, irritable bowel syndrome, constipation, neck pain** (44,51); **premenstrual syndrome, chronic pelvic pain, pelvic inflammatory disease, metrorrhagia, endometriosis** (52); feelings of **sadness, sleeping disorders** (53); **panic disorder, substance abuse, drug abuse, personality disorders** (44); **osteoarthritis, gastritis, varices, arthritis, spondylarthritis, thyroid disease, colitis, gall stones, chronic bronchitis, pyelonephritis, coronary disease, venous thrombosis, peptic ulcers, nephrolithiasis, osteoporosis, heart failure, hepatitis, non-insulin dependent diabetes mellitus, cancer, cerebrovascular disease, stroke** (50).

Diseases negatively or not associated with LBP: **alcohol abuse** (44,54); **chronic obstructive pulmonary disease** (49); **myocardial infarction** (50,51); **insulin dependent diabetes mellitus, meningitis** (50).

Diseases with conflicting evidence regarding a possible positive or negative association with LBP: **arterial hypertension, peripheral arterial disease** (50,51).

Disease with no research on possible association with LBP: **hyperventilation** (49).

Diseases positively associated with sciatica: **atherosclerosis** (55); **tobacco use** (56,57); **overweight, obesity** (57,58).

Diseases negatively or not associated with sciatica: **arterial hypertension, dyslipidaemia** (57).

ICPC-2-codes for all of the diseases noted above: P76 P01 P74 P17 K92 R02 R96 A92 F71 R97 S87 S88 S98 A70 R71 R72 R73 R74 R75 R76 R77 R78 R79 R80 R81 R82 R83 P75 N01 N85 N89 K74 K99 D93 D12 L01 L83 X89 X17 X74 X08 X99 P03 P06 P74 P15 P16 P17 P18 P19 P80 L89 L90 L91 D02 D03 D87 K06 K95 L87 L88 T71 T72 T78 T81 T85 T86 D70 D73 D92 D94 D98 U70 K94 D85 D86 U95 L95 K77 D72 D13 D23 D97 T90 A79 B72 B73 B74 D74 D75 D76 D77 F74 H75 K72 L71 K74 R84 R85 S77 S78 T71 U75 U76 U77 W72 X75 X76 X77 Y77 Y78 K91 K89 K90 R95 K75 T89 N71 K85 K86 K87 R98 T82 T83.

Supplement III: pharmacotherapeutic agents

Pharmacotherapeutic agents used in the treatment of LBP and sciatica: paracetamol, NSAIDs, benzodiazepines, antiepileptics, opioids, antidepressants (59–61)

The respective ATC codes of the aforementioned agents: N02BE01 M01A N05CD N05BA N03AE N03A N02A N06A (28).

Supplement IV: Trends in comorbidities of patients with LBP without irradiation (2001- 2020)

Here, we print the full table with all comorbid diagnoses for patients with an L86 diagnosis for each given timespan, including the p-value for a possible trend. However, when the absolute number of comorbid diagnoses is small, there is insufficient power to draw firm conclusions about this trend and therefore, the printed p-value is irrelevant.

Totals	2001-2004	2005-2008	2009-2012	2013-2016	2017-2020	p-value
Patients with LBP	3683	4554	4861	4876	10132	0
mean age ± SD, years	52.3 (15.9)	53.4 (16.1)	53 (15.9)	53.3 (16.3)	53.8 (16.4)	0.0004
women, N (%)	1928 (52.3%)	2467 (54.2%)	2635 (54.2%)	2739 (56.2%)	5553 (54.8%)	0.0089
Illnesses (ICPC-2 and official designation)						
A70 Tuberculosis	1 (0%)	3 (0.1%)	3 (0.1%)	3 (0.1%)	6 (0.1%)	0.6679
A79 Malignancy NOS	25 (0.7%)	34 (0.7%)	34 (0.7%)	45 (0.9%)	66 (0.7%)	0.8856
A92 Allergy/Allergic reaction NOS	15 (0.4%)	22 (0.5%)	22 (0.5%)	46 (0.9%)	131 (1.3%)	<0.0001
B72 Lymphoma	6 (0.2%)	6 (0.1%)	8 (0.2%)	29 (0.6%)	38 (0.4%)	0.0006
B73 Leukaemia	1 (0%)	8 (0.2%)	6 (0.1%)	11 (0.2%)	29 (0.3%)	0.0019
B74 Malignant neoplasm blood other	5 (0.1%)	1 (0%)	1 (0%)	4 (0.1%)	7 (0.1%)	0.8105
D02 Abdominal pain epigastric	8 (0.2%)	13 (0.3%)	11 (0.2%)	28 (0.6%)	51 (0.5%)	0.0013
D03 Heartburn	4 (0.1%)	4 (0.1%)	18 (0.4%)	15 (0.3%)	20 (0.2%)	0.2036
D12 Constipation	14 (0.4%)	46 (1%)	37 (0.8%)	79 (1.6%)	237 (2.3%)	<0.0001
D13 Jaundice	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
D23 Hepatomegaly	0 (0%)	0 (0%)	0 (0%)	2 (0%)	3 (0%)	0.0799
D70 Gastrointestinal infection	0 (0%)	1 (0%)	1 (0%)	4 (0.1%)	39 (0.4%)	<0.0001
D72 Viral hepatitis	2 (0.1%)	3 (0.1%)	2 (0%)	4 (0.1%)	18 (0.2%)	0.0126
D73 Gastroenteritis presumed infection	17 (0.5%)	17 (0.4%)	33 (0.7%)	27 (0.6%)	18 (0.2%)	0.0076
D74 Malignant neoplasm stomach	2 (0.1%)	5 (0.1%)	8 (0.2%)	11 (0.2%)	10 (0.1%)	0.558
D75 Malignant neoplasm colon/rectum	13 (0.4%)	39 (0.9%)	52 (1.1%)	114 (2.3%)	1001 (9.9%)	<0.0001

D76 Malignant neoplasm pancreas	0 (0%)	0 (0%)	4 (0.1%)	8 (0.2%)	16 (0.2%)	0.0004
D77 Malignant digestive neoplasm other/NOS	4 (0.1%)	11 (0.2%)	17 (0.3%)	30 (0.6%)	67 (0.7%)	<0.0001
D85 Duodenal ulcer	0 (0%)	6 (0.1%)	0 (0%)	2 (0%)	1 (0%)	0.1497
D86 Peptic ulcer other	5 (0.1%)	5 (0.1%)	2 (0%)	2 (0%)	12 (0.1%)	0.8672
D87 Stomach function disorder	69 (1.9%)	131 (2.9%)	157 (3.2%)	190 (3.9%)	377 (3.7%)	<0.0001
D92 Diverticular disease	5 (0.1%)	12 (0.3%)	13 (0.3%)	16 (0.3%)	27 (0.3%)	0.2669
D93 Irritable bowel disease	345 (9.4%)	455 (10%)	579 (11.9%)	681 (14%)	1146 (11.3%)	<0.0001
D94 Chronic enteritis/ulcerative colitis	67 (1.8%)	83 (1.8%)	89 (1.8%)	119 (2.4%)	138 (1.4%)	0.0824
D97 Liver disease NOS	74 (2%)	81 (1.8%)	113 (2.3%)	201 (4.1%)	389 (3.8%)	<0.0001
D98 Cholecystitis/cholelithiasis	20 (0.5%)	12 (0.3%)	22 (0.5%)	29 (0.6%)	68 (0.7%)	0.0176
F71 Conjunctivitis allergic	2 (0.1%)	2 (0%)	1 (0%)	8 (0.2%)	27 (0.3%)	<0.0001
F74 Neoplasm of eye/adnexa	0 (0%)	3 (0.1%)	1 (0%)	4 (0.1%)	8 (0.1%)	0.1005
H75 Neoplasm of ear	0 (0%)	1 (0%)	3 (0.1%)	4 (0.1%)	3 (0%)	0.4237
K06 Prominent veins	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (0.1%)	0.0094
K72 Neoplasm cardiovascular	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0.308
K74 Ischaemic heart disease with angor	131 (3.6%)	169 (3.7%)	137 (2.8%)	167 (3.4%)	274 (2.7%)	0.0022
K75 Acute myocardial infarction	7 (0.2%)	8 (0.2%)	13 (0.3%)	27 (0.6%)	18 (0.2%)	0.5882
K77 Heart failure	44 (1.2%)	45 (1%)	36 (0.7%)	46 (0.9%)	161 (1.6%)	0.0025
K85 Elevated blood pressure	0 (0%)	3 (0.1%)	1 (0%)	0 (0%)	13 (0.1%)	0.0116
K86 Hypertension uncomplicated	648 (17.6%)	890 (19.5%)	1007 (20.7%)	1108 (22.7%)	2448 (24.2%)	<0.0001
K87 Hypertension complicated	9 (0.2%)	9 (0.2%)	16 (0.3%)	19 (0.4%)	47 (0.5%)	0.0068
K89 Transient cerebral ischaemia	8 (0.2%)	12 (0.3%)	9 (0.2%)	14 (0.3%)	25 (0.2%)	0.7354
K90 Stroke/cerebrovascular accident	66 (1.8%)	88 (1.9%)	100 (2.1%)	113 (2.3%)	230 (2.3%)	0.0384
K91 Cerebrovascular disease	8 (0.2%)	3 (0.1%)	12 (0.2%)	15 (0.3%)	129 (1.3%)	<0.0001

K92 Atherosclerosis/peripheral vascular disease	105 (2.9%)	139 (3.1%)	151 (3.1%)	153 (3.1%)	301 (3%)	0.8721
K94 Phlebitis/thrombophlebitis	21 (0.6%)	33 (0.7%)	32 (0.7%)	27 (0.6%)	54 (0.5%)	0.3182
K95 Varicose veins of leg	26 (0.7%)	44 (1%)	53 (1.1%)	66 (1.4%)	148 (1.5%)	<0.0001
K99 Cardiovascular disease other	9 (0.2%)	15 (0.3%)	37 (0.8%)	56 (1.1%)	75 (0.7%)	<0.0001
L01 Neck symptom/complaint	2 (0.1%)	2 (0%)	2 (0%)	7 (0.1%)	93 (0.9%)	<0.0001
L71 Malignant neoplasm musculoskeletal	3 (0.1%)	0 (0%)	3 (0.1%)	3 (0.1%)	7 (0.1%)	0.5469
L83 Neck syndrome	195 (5.3%)	305 (6.7%)	378 (7.8%)	461 (9.5%)	562 (5.5%)	0.9454
L87 Bursitis/tendinitis/synovitis NOS	46 (1.2%)	61 (1.3%)	77 (1.6%)	91 (1.9%)	227 (2.2%)	<0.0001
L88 Rheumatoid/seropositive arthritis	55 (1.5%)	62 (1.4%)	88 (1.8%)	81 (1.7%)	186 (1.8%)	0.0576
L89 Osteoarthritis of hip	139 (3.8%)	190 (4.2%)	194 (4%)	204 (4.2%)	430 (4.2%)	0.281
L90 Osteoarthritis of knee	201 (5.5%)	328 (7.2%)	394 (8.1%)	418 (8.6%)	727 (7.2%)	0.0073
L91 Osteoarthritis other	363 (9.9%)	541 (11.9%)	562 (11.6%)	689 (14.1%)	1202 (11.9%)	
L95 Osteoporosis	140 (3.8%)	191 (4.2%)	197 (4.1%)	199 (4.1%)	394 (3.9%)	0.8117
N01 Headache	1 (0%)	5 (0.1%)	5 (0.1%)	14 (0.3%)	44 (0.4%)	<0.0001
N71 Meningitis/encephalitis	1 (0%)	1 (0%)	0 (0%)	1 (0%)	3 (0%)	0.7388
N85 Congenital anomaly neurological	6 (0.2%)	7 (0.2%)	8 (0.2%)	11 (0.2%)	6 (0.1%)	0.1184
N89 Migraine	182 (4.9%)	233 (5.1%)	322 (6.6%)	356 (7.3%)	799 (7.9%)	<0.0001
P01 Feeling anxious/nervous/tense	4 (0.1%)	5 (0.1%)	5 (0.1%)	10 (0.2%)	21 (0.2%)	0.0651
P03 Feeling depressed	1 (0%)	1 (0%)	6 (0.1%)	10 (0.2%)	38 (0.4%)	<0.0001
P06 Sleep disturbance	6 (0.2%)	13 (0.3%)	12 (0.2%)	20 (0.4%)	128 (1.3%)	<0.0001
P15 Chronic alcohol abuse	54 (1.5%)	60 (1.3%)	89 (1.8%)	129 (2.6%)	215 (2.1%)	<0.0001
P16 Acute alcohol abuse	2 (0.1%)	0 (0%)	0 (0%)	2 (0%)	8 (0.1%)	0.0944
P17 Tobacco abuse	53 (1.4%)	88 (1.9%)	103 (2.1%)	192 (3.9%)	579 (5.7%)	<0.0001
P18 Medication abuse	2 (0.1%)	3 (0.1%)	3 (0.1%)	3 (0.1%)	20 (0.2%)	0.0076

P19 Drug abuse	1 (0%)	2 (0%)	4 (0.1%)	5 (0.1%)	27 (0.3%)	<0.0001
P74 Anxiety disorder/anxiety state	13 (0.4%)	26 (0.6%)	18 (0.4%)	17 (0.3%)	128 (1.3%)	<0.0001
P75 Somatisation disorder	7 (0.2%)	16 (0.4%)	14 (0.3%)	12 (0.2%)	32 (0.3%)	0.5422
P76 Depressive disorder	95 (2.6%)	87 (1.9%)	117 (2.4%)	120 (2.5%)	380 (3.8%)	<0.0001
P80 Personality disorder	10 (0.3%)	14 (0.3%)	16 (0.3%)	31 (0.6%)	173 (1.7%)	<0.0001
R02 Shortness of breath/dyspnoea	5 (0.1%)	6 (0.1%)	10 (0.2%)	4 (0.1%)	44 (0.4%)	0.0003
R71 Whooping cough	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
R72 Strep throat	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
R73 Boil/abscess nose	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
R74 Upper respiratory tract infection acute	62 (1.7%)	51 (1.1%)	88 (1.8%)	125 (2.6%)	107 (1.1%)	0.1829
R75 Sinusitis acute/chronic	24 (0.7%)	33 (0.7%)	37 (0.8%)	46 (0.9%)	100 (1%)	0.0192
R76 Tonsillitis acute	2 (0.1%)	4 (0.1%)	4 (0.1%)	7 (0.1%)	12 (0.1%)	0.228
R77 Laryngitis/tracheitis acute	9 (0.2%)	8 (0.2%)	12 (0.2%)	5 (0.1%)	7 (0.1%)	0.0044
R78 Acute bronchitis/bronchiolitis	54 (1.5%)	58 (1.3%)	74 (1.5%)	71 (1.5%)	86 (0.8%)	0.0015
R79 Chronic bronchitis	86 (2.3%)	103 (2.3%)	85 (1.7%)	78 (1.6%)	116 (1.1%)	<0.0001
R80 Influenza	22 (0.6%)	26 (0.6%)	27 (0.6%)	25 (0.5%)	102 (1%)	0.0017
R81 Pneumonia	6 (0.2%)	11 (0.2%)	17 (0.3%)	14 (0.3%)	42 (0.4%)	0.0168
R82 Pleurisy/pleural effusion	0 (0%)	3 (0.1%)	1 (0%)	2 (0%)	3 (0%)	0.8593
R83 Respiratory infection other	8 (0.2%)	6 (0.1%)	6 (0.1%)	8 (0.2%)	21 (0.2%)	0.6235
R84 Malignant neoplasm bronchus/lung	3 (0.1%)	20 (0.4%)	15 (0.3%)	38 (0.8%)	41 (0.4%)	0.0123
R85 Malignant neoplasm respiratory other	1 (0%)	4 (0.1%)	4 (0.1%)	12 (0.2%)	9 (0.1%)	0.2104
R95 Chronic obstructive pulmonary disorder	117 (3.2%)	196 (4.3%)	181 (3.7%)	191 (3.9%)	500 (4.9%)	<0.0001
R96 Asthma	302 (8.2%)	432 (9.5%)	582 (12%)	690 (14.2%)	1348 (13.3%)	<0.0001
R97 Allergic rhinitis	30 (0.8%)	41 (0.9%)	53 (1.1%)	54 (1.1%)	190 (1.9%)	<0.0001

R98 Hyperventilation syndrome	32 (0.9%)	22 (0.5%)	23 (0.5%)	47 (1%)	93 (0.9%)	0.0338
S77 Malignant neoplasm of skin	39 (1.1%)	41 (0.9%)	57 (1.2%)	88 (1.8%)	196 (1.9%)	<0.0001
S78 Lipoma	1 (0%)	2 (0%)	2 (0%)	4 (0.1%)	13 (0.1%)	0.0206
S87 Dermatitis/atopic eczema	254 (6.9%)	409 (9%)	500 (10.3%)	496 (10.2%)	494 (4.9%)	<0.0001
S88 Dermatitis contact/allergic	172 (4.7%)	240 (5.3%)	290 (6%)	357 (7.3%)	1032 (10.2%)	<0.0001
S98 Skin disease other	23 (0.6%)	21 (0.5%)	51 (1%)	45 (0.9%)	90 (0.9%)	0.0222
T71 Malignant neoplasm thyroid	0 (0%)	5 (0.1%)	5 (0.1%)	3 (0.1%)	14 (0.1%)	0.0758
T72 Benign neoplasm thyroid	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0.6035
T78 Thyroglossal duct/cyst	7 (0.2%)	9 (0.2%)	8 (0.2%)	18 (0.4%)	10 (0.1%)	0.3627
T81 Goitre	54 (1.5%)	63 (1.4%)	90 (1.9%)	88 (1.8%)	164 (1.6%)	0.3423
T82 Obesity	9 (0.2%)	31 (0.7%)	18 (0.4%)	35 (0.7%)	137 (1.4%)	<0.0001
T83 Overweight	0 (0%)	0 (0%)	1 (0%)	5 (0.1%)	23 (0.2%)	<0.0001
T85 Hyperthyroidism/thyrotoxicosis	3 (0.1%)	10 (0.2%)	13 (0.3%)	11 (0.2%)	34 (0.3%)	0.0147
T86 Hypothyroidism/myxoedema	48 (1.3%)	69 (1.5%)	91 (1.9%)	135 (2.8%)	384 (3.8%)	<0.0001
T89 Diabetes insulin resistant	27 (0.7%)	33 (0.7%)	29 (0.6%)	31 (0.6%)	68 (0.7%)	0.6689
T90 Diabetes non-insulin resistant	193 (5.2%)	305 (6.7%)	411 (8.5%)	608 (12.5%)	1000 (9.9%)	<0.0001
U70 Pyelonephritis/pyelitis	2 (0.1%)	4 (0.1%)	4 (0.1%)	4 (0.1%)	11 (0.1%)	0.3866
U75 Malignant neoplasm of kidney	6 (0.2%)	9 (0.2%)	3 (0.1%)	5 (0.1%)	20 (0.2%)	0.6896
U76 Malignant neoplasm of bladder	5 (0.1%)	8 (0.2%)	13 (0.3%)	21 (0.4%)	14 (0.1%)	0.8375
U77 Malignant neoplasm urinary tract other	0 (0%)	4 (0.1%)	4 (0.1%)	5 (0.1%)	3 (0%)	0.9274
U95 Urinary calculus	10 (0.3%)	14 (0.3%)	22 (0.5%)	20 (0.4%)	61 (0.6%)	0.0029
W72 Malignant neoplasm related to pregnancy	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	0.3127
X08 Intermenstrual bleeding	7 (0.2%)	6 (0.1%)	9 (0.2%)	7 (0.1%)	13 (0.1%)	0.4695
X17 Pelvis symptom/complaint	0 (0%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0.3414

female						
X74 Pelvic inflammatory disease	0 (0%)	1 (0%)	2 (0%)	0 (0%)	3 (0%)	0.5376
X75 Malignant neoplasm cervix	5 (0.1%)	11 (0.2%)	18 (0.4%)	23 (0.5%)	704 (6.9%)	<0.0001
X76 Malignant neoplasm breast female	25 (0.7%)	56 (1.2%)	103 (2.1%)	161 (3.3%)	314 (3.1%)	<0.0001
X77 Malignant neoplasm genital female other	10 (0.3%)	13 (0.3%)	24 (0.5%)	23 (0.5%)	32 (0.3%)	0.6787
X89 Premenstrual tension syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	0.0662
X99 Genital disease female other	11 (0.3%)	6 (0.1%)	14 (0.3%)	19 (0.4%)	37 (0.4%)	0.073
Y77 Malignant neoplasm prostate	18 (0.5%)	33 (0.7%)	37 (0.8%)	46 (0.9%)	95 (0.9%)	0.0064
Y78 Malignant neoplasm male genital other	4 (0.1%)	3 (0.1%)	2 (0%)	1 (0%)	5 (0%)	0.2065

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