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The epidemiology of knee osteoarthritis in general practice: a registry-based study

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Abstract

Objectives The present study investigated (i) trends in the prevalence and incidence of knee osteoarthritis over a 20-year period; (ii) trends in comorbidity; and (iii) trends in drug prescriptions.

Design Registry-based study.

Setting Primary health care, Flanders, Belgium.

Participants Data were collected from Intego, a general practice-based morbidity registration network. In the study period between 1996 and 2015 data from 440,140 unique patients were available.

Outcome measures International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) were used to classify diagnoses in Intego. Trends in prevalence and incidence rate of knee osteoarthritis were computed using joinpoint regression analysis. The mean disease count was calculated to assess trends in comorbidity. In addition, the number of drug prescriptions was identified by the Anatomical Therapeutic Chemical Classification code and trends were equally recorded with joinpoint regression.

Results The prevalence of knee osteoarthritis increased from 1.99% in 1996 to 3.56% in 2015. An upward trend was observed with an average annual percentage change (AAPC) of 2.5 (95%CI 2.2-2.9). The incidence remained stable with 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5). The mean disease count significantly increased from 1.63 to 2.34 ($p<0.001$) for incident cases with knee osteoarthritis. Finally, we observed a significantly positive trend in the overall prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1).

Conclusions Increased prevalence, comorbidity, and number of drug prescriptions confirm an increased burden of knee osteoarthritis. In future, these trends can be used to prioritize initiatives for improvement in care.

Key Words

Knee osteoarthritis; multimorbdity; general practice; trends; burden of illness

Article Summary

Strengths and limitations of this study

- The Intego open registry provides real-world data of 440,140 unique patients in a primary care setting, representative for the Flemish population.
- This registry database, with data over a 20-year time period (1996-2015), lends itself perfectly for trend analyses.
- Estimates on the prevalence and incidence of knee osteoarthritis are scarce for primary care settings. This study defines knee osteoarthritis when it becomes a healthcare problem for the patient.
- Data completeness depends on the quality of registration of the participating general practitioners. To this end, only optimal registration practices are included in the Intego database.
- The lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes.

Introduction

Osteoarthritis (OA) is the most commen joint disease and is expected to become the fourth leading cause of disability worldwide by 2020.[1] OA mainly affects the joints of the knees, hips, hands, facets and feet, but knee OA accounts for 83% of the total OA burden.[2] The prevalence of knee OA varies according to the definition: from subjective (population-based) assessments to clinical and radiographic definitions, often with low levels of concordance between them.[3] However, estimates on the prevalence of knee OA are scarce for primary care settings.[4]

At present, the purposes of conservative knee OA treatment are to alleviate pain, to improve the function of the joint and to slow down joint damage by pharmacological and non-pharmacological means.[5] Pharmacological management is dominated both by acetaminophen and by nonsteroidal anti-inflammatory drugs (NSAIDs).[5-8] Although the review by Machado et al. suggested that acetaminophen has little clinical benefit in OA, guidelines recommend starting with acetaminophen, because the adverse side effect profile of NSAIDs.[9] The presence of comorbidities may also affect choices in the pharmacological management.[10-12] Almost all patients with OA suffer from at least one comorbid disease.[13] Common comorbidities in patients with knee OA are cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and obesity.[14] Nevertheless, comorbidity-adapted management protocols are being developed and provide tailored guidance for pharmacological management and exercise therapy.[5 8]

The aims of the present study were 1) to evaluate time trends in the prevalence and incidence of patients with knee OA managed in general practice; 2) to assess trends in the comorbid burden and 3) to assess trends in drug prescriptions over a 20-year period. Hence, we extracted “real world” data from the Belgian primary care-based Intego patient register. Important attributes of most patient registries are

their large sample size and data variability.[15] The health trends from the Intego register aim to be hypothesis generating rather than hypothesis testing and can be used to prioritize initiatives for improvement in care.

Methods

Design and participants

This trend analysis study was performed using Intego, a general practice-based morbidity registration network in Flanders, Belgium.[16] The Intego database comprises data extracted from electronic health records (EHR) of general practitioners (GPs), all using the medical software programme Medidoc (Corilus NV, Aalter, Belgium).[17] In 2015, 111 GPs of 48 practices evenly spread throughout Flanders, collaborated in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The selection procedure was described in detail previously.[16] The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results, some background information (including gender and year of birth) and some biomedical parameters (i.e. blood pressure, height, weight, smoking status and mortality), using computer-generated keywords internally linked to codes. With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and chronologically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus and automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[18] Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.[19]

Intego started to collect data in 1994. Data were accumulated on a yearly basis and the number of participating general practices increased from 26 (i.e. 34 GPs) in 1999 to 48 (i.e. 111 GPs) in 2015. Since the start of the registration, hardly any GPs stopped collaboration with Intego.

Data collection

For the present study, data over a 20-year time interval from 1 January 1996 to 31 December 2015 were used. In this period, 440,140 unique patients were registered in the Intego database. This study was reported in accordance with the RECORD checklist specific to observational studies using routinely collected health data.[20] Extracted data concerned data on prevalence, incidence, clinical characteristics of patients (e.g. comorbidity) and pharmacotherapy.

Data on prevalence and incidence

The prevalence of a population is the proportion of the population with the disease at a specified time. Unlike incidence rates, which focus on new events, prevalence focuses on existing states. Because of the design of Intego (no episode registration and no recording of cure) prevalence rates could only be calculated on incurable chronic diseases, such as knee osteoarthritis.[16] Data for the first registration of prevalent diseases were routinally registered in Intego from 1994 and historically accumulated if registered in an earlier period.

Calculating disease prevalence requires both a numerator (number of persons with a disease) and a matching denominator (the 'population at risk' being studied). Determining primary care practice denominators is challenging.[21] The yearly contact group (YCG) is the set of patients with a visit noted in the electronic medical records during the past year. In this study, the YCG was used as denominator for all time trend analyses.[22]

Data on comorbidity

Patients' medical history before they presented with knee OA was registered for all cases between 1996 and 2015. A disease count was calculated for all incident cases with knee OA. For this disease count, a list of chronic diseases based on the paper by Knottnerus et al was used.[23] For the presence of chronic kidney disease (CKD), the glomerular filtration rate (GFR) was based on the closest creatinine measurement in the two years before or after presentation with knee OA diagnosis (Supplementary file 1: ICPC codes for diagnosis and comorbidity).

Data on drug prescriptions

The prescription of medication for knee OA, including acetaminophen, oral and topical anti-inflammatory drugs, cox-2 selective anti-inflammatory drugs, weak and strong opioids, parenteral glucocorticoids, parenteral hyaluronic acid and glucosamine was extracted from Intego for all prevalent cases with knee OA (Supplementary file 2: used ACT codes). Prescription of medication was considered positive if it was prescribed at least once a year.

Statistical analysis

Descriptive statistics, with frequency distribution and percentages, were used to measure the prevalence (/100 patients) and incidence (/1000 patient years at risk) of patients with knee OA. Data were stratified by gender and ten-year age cohorts, starting from 25 with 85 years and older as the last cohort. The rates were age-standardized by taking the Flemish population of the year 1996 as reference population.[24] Additionally, possible time trends were analysed in the age-standardized cohorts with joinpoint regression analysis.[25] Joinpoint analysis identifies the best-fitting point, where a statistically significant change (called the "joinpoint") occurs, and determines the trends between joinpoints. Joinpoint regression allows us to identify the time point(s) of follow-up at which trends significantly change.[26] The annual percentage change (APC) is proposed to summarize and compare the rates of changes

between successive change points.[27] In the final model, the joinpoint analysis also provides an average annual percentage change (AAPC) as an average of APC estimates.[27] Analysis was performed with the Joinpoint Regression Program (version 3.5.3, released in May 2013 and available at http://surveillance.cancer.gov/joinpoint). This program starts with the minimum number of joinpoint (e.g. zero joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model. This enables the user to test that an apparent change in trend is statistically significant.

Trends in the comorbidity profile for incident cases with knee OA were explored over four time intervals of five years (1996-2000, 2001-2005, 2006-2010 and 2011-2015) by the Cochran-Armitage test and the Jonckheere-Terpstra test. The Cochran-Armitage test for trend analysis is a modified Pearson's chi-square test to assess the association between binary and ordinal categeries (e.g. between comorbidities and time intervals). The Jonckheere-Terpstra trend test was used to analyse trends for continuous variables (e.g. between age and time intervals).[28]

Over the same 20-year time period, trends in drug prescriptions for prevalent cases with knee OA were analyzed using joinpoint regression analysis, as described above. Two-sided p-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using R Software Version 3.3.2 (Free Software Foundation Inc., Boston, MA, USA).

Patient involvement

No patients were involved in defining the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of the results.

Results

Demographic characteristics and trends in the prevalence and incidence of patients with knee osteoarthritis (1996-2015)

Between 1 January 1996 and 31 December 2015, the Intego database incluced data on 440,140 unique patients. Table 1 shows the demographic characteristics of the patients with knee OA by gender and age cohorts in Table 1.The age-standardized prevalence of knee OA increased by 79% from 1.99% in 1996 to 3.56% in 2015 (AAPC= 2.5, 95%CI 2.2-2.9, Figure 1). Woman have a higher prevalence than men do, but over the 20 years of the study men have a higher relative increase in prevalence (AAPC= 3.1, 95%CI 2.7-3.5 for men versus AAPC= 2.4, 95%CI 2.0-2.7 for women). Figure 2 presents the observed and modeled long-term time trends in prevalence by gender. The age-standardized incidence of patients with knee OA remained stable with 4.23‰ in 1996 and 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5), but showed a positive trend between 2006 and 2015 from 3.05‰ to 3.75‰, respectively (APC= 1.9,

95%CI 0.4-3.5) (Figure 3). Between 2006 and 2015, this positive trend was higher for men (APC= 2.5, 95%CI 0.5-4.5) than for women (APC= 1.9, 95%CI 0.4-3.5) (Figure 3).

Trends in comorbidity in newly diagnosed patients with knee osteoarthritis (1996-2015)

In the 20-year study period, the mean age at diagnosis of knee OA remained stable (p=0.384) with 55.3 years in 1996 and 56.9 years in 2015, respectively, while a non-significant decline was found in the proportion of women in this period (65% to 62%, p=0.052). Additionally, the disease burden was defined by calculating the mean disease count of patients with knee OA.[23] This mean disease count showed a significant increase in the study period ranging from 1.6 to 2.3 (p<0.001), meaning that the comorbid burden of patients with knee OA increased. In this study, the following comorbidities increased significantly: the proportions of patients with diabetes (6% to 15%, p<0.001), cardiovascular events (21% to 27%, p<0.001), depression (9% to 13%, p=0.009) and obesity (5% to 8%, p<0.001). Hypertension, gastro-intestinal ulcer and renal failure remained stable. Additionally, we noted that the proportion of knee OA patients with cancer (2% to 3%, p<0.001), asthma (8% to 17%, p<0.001) and substance abuse (0% to 2%, p<0.001) increased significantly during the study period, while the proportion with osteoporosis remained stable (Table 2).

Trends in prescriptions for patients with knee osteoarthritis (1996-2015)

The prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1) for patients with knee OA increased during the study period (Table 3). The prevalence of patients with knee OA who were prescribed acetaminophen was lower than those with oral NSAIDs (19.2% versus 29.4% in 2015; 5.3% versus 28.4% in 1996). The prescription of oral, topical and cox-2 selective NSAIDs remained stable for both genders during the study period. The use of strong opioids showed a strong increase between 1996 and 2003 (AAPC= 9.0, 95%CI 2.5-16), but then decreased slightly in the period from 2003 to 2015 (AAPC= -2.0, 95%CI 3.7 to -0.3).

Discussion

This study presents estimates of knee OA prevalence and incidence based on a large morbidity registration network for general practice in Belgium. During the 20-year study period, the age-standardized prevalence of knee OA significantly increased while the age-standardized incidence rate remained stable. During the study period, patients with knee OA sufferered from more comorbidities, as shown by almost a doubling of the disease count. Oral NSAIDs were most frequently prescribed for the prevalent patients with knee OA, while prescription of acetaminophen, weak opioids and glucosamine showed an overall positive trend.

This study shows that the prevalence rate of knee OA significantly increased even after standardization of the study population. General practice morbidity registration networks in other European countries

show similar rates for knee OA: in the Netherlands, an overall prevalence of 3.4% and incidence of 3.2‰ was registered in 2016.[29] In our study, we found similar rates with 3.56% and 3.75‰ respectively for the year 2015. In the UK, the estimated proportion of people who sought treatment for knee OA is high: 18% of the population aged 45 and over consulted their GP for knee OA.[30] In our study, we found a consultation prevalence of 21% for the same reference year (2010) and age cohorts. The latter study also found that OA is the most common musculoskeletal condition in older people and that just over half of all patients consulting their GP about OA have knee OA. In the near future, the number of people with knee OA is expected to rise considerably because of an aging population and obesity trends.[31] Nevertheless, the increasing prevalence of knee OA in general practice registration could also be attributed to other factors, for example: better access to general practice, more awareness of the public of preventive medicine, better diagnostics, better registration and higher demands and expectations of older people to remain physically active. Future qualitative research with different stakeholders could assess these possible explanations.

Osteoarthritis is one of the diseases with the highest rate of comorbidity, with reported rates of 68% to 85%.[13 14] Diseases that frequently occur next to OA are diabetes, hypertension, atherosclerotic heart disease, overweight, and back pain.[32] Coexisting disorders may worse pain and bring additional impairments, which necessitate adaptations to the conservative management of knee OA.[33 34] In our study, knee OA was also strongly associated with the following comorbidities: asthma, cancer, depression and substance abuse. The substantial contribution of OA to multi-morbidity and frailty should be recognized, further investigated, and needs extra attention in general practice management of long-term conditions.

Pharmacological management of knee OA in general practice is dominated both by acetaminophen and by NSAIDs, as they are both recommended in evidence-based guidelines.[5-8] In our study, NSAIDs were the most frequently prescribed pain drug for prevalent patients with knee OA. Verkleij et al. observed the effects of medication on 104 patients with knee OA in general practice. They demonstrated no significant difference regarding knee pain and knee function between patients taking diclofenac or acetaminophen.[35] If acetaminophen should remain the ‘’first-line’ treatment for patients with a new episode, the effects of acetaminophen and the role in patients with comorbidities should be further investigated.[36]

Strenghts and limitations

The major strengths of this study are the long-term follow-up data of a practice-based morbidity registration network in general practice. Intego covers more than 2% of the Flemish population, highly representative for age and gender. Longitudinal data in registry-based studies are used to track the natural history of diseases over time and enable us to perform time-to-event analyses. A few limitations must also be considered. Lack of data verification is a common problem in registry-based studies with

longitudinal data of large sample size. In Intego, the lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes with a detalled thesaures, individual patients are followed over time and their history is taken into account. If diagnoses are not mutually exclusive, then they count for one. Secondly, we are aware that accurate coding is always a risk for possible underdiagnosis. The difference between early-onset knee OA and chronic, established knee OA can not be established with the ICPC codes. Standardized coding for OA should be adopted in general practice to accurately describe the extent of the condition and to maximize the conservative management options to improve quality of life. Furthermore, there is no obligation for patients to be registered with a particular GP in Belgium. Therefore, it can be difficult to define 'the population at risk' for epidemiological studies in general practice. In Intego, the YCG was used as denominator for all trend analyses. Importantly, mortality data are lacking in Intego. Therefore, patients in the incidence analysis are considered at risk until the diagnosis or until December 31 of any specific year to compensate for possible overestimation in this registry-based study. Finally, obesity could not be reliably assessed from the Intego database, because of insufficient registration of up-to-date weight and height in medical health records. Quality improvement initiatives should make GPs more aware of the necessity of properly recording up-to-date patient variables, such as BMI, in the EHR because of their growing importance in patient-tailored management strategies. Patient portals and remote access to their own medical health record are future initiatives, where the patient could play a more central role to help the GP in keeping these parameters more up-to-date by shared responsibility.[37]

Conclusion and recommendations

In conclusion, increased prevalence, comorbidity, and number of drug prescriptions, together with the young age at incidence, confirm the high burden of knee OA. Our registry-based study represents knee OA diagnoses at a time it becomes a health issue for patients. Professionals face more difficulties in their conservative management options due to rising comorbidity. In future, these health trends can be used to prioritize initiatives for improvement in care.

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References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/S0140-6736(12)61689-4

2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2

3. Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185-99. doi: 10.1093/bmb/lds038

4. Bedson J, Jordan K, Croft P. The prevalence and history of knee osteoarthritis in general practice: a case-control study. *Fam Pract* 2005;22(1):103-8. doi: 10.1093/fampra/cmh700 [published Online First: 2005/01/11]

5. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22(3):363-88. doi: 10.1016/j.joca.2014.01.003 [published Online First: 2014/01/28]

6. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64(4):465-74. [published Online First: 2012/05/09]

7. Kingsbury SR, Gross HJ, Isherwood G, et al. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014;53(5):937-47. doi: 10.1093/rheumatology/ket463 [published Online First: 2014/02/04]

8. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72(7):1125-35. doi: 10.1136/annrheumdis-2012-202745 [published Online First: 2013/04/19]

9. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *Bmj* 2015;350:h1225. doi: 10.1136/bmj.h1225 [published Online First: 2015/04/02]

10. Harding PA, Holland AE, Hinman RS, et al. Physical activity perceptions and beliefs following total hip and knee arthroplasty: a qualitative study. *Physiother Theory Pract* 2015;31(2):107-13. doi: 10.3109/09593985.2014.959581 [published Online First: 2014/12/17]

11. National Institute for Health and Care Excellence (NICE): Osteoarthritis: care and management (quality standard 87).2019 http://guidance.nice.org.uk/qs87

12. de Rooij M, Steultjens MPM, Avezaat E, et al. Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity. *Physical Therapy Reviews* 2013;18(2):101-11. doi: 10.1179/1743288X12Y.0000000056

13. van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord* 2008;9:95. doi: 10.1186/1471-2474-9-95 [published Online First: 2008/06/28]

14. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2017;69(6):807-16. doi: 10.1002/acr.23013 [published Online First: 2016/08/27]

15. Trotter JP. Patient registries: a new gold standard for "real world" research. *Ochsner J* 2002;4(4):211-4. [published Online First: 2002/10/01]

16. Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48. doi: 10.1186/1472-6947-14-48 [published Online First: 2014/06/08]

17. Vanbeselaere V, Truyers C, Elli S, et al. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. *BMC Cardiovasc Disord* 2016;16:61. doi: 10.1186/s12872-016-0235-1 [published Online First: 2016/03/30]

18. Okkes IM, Becker HW, Bernstein RM, et al. The March 2002 update of the electronic version of ICPC-2. A step forward to the use of ICD-10 as a nomenclature and a terminology for ICPC-2. *Fam Pract* 2002;19(5):543-6. [published Online First: 2002/10/03]

19. WHO Collaborating Centre for Drug Statistics Methodology: ATC/DDD Index 2010. http://www.whocc.no/atc_ddd_index

20. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]

21. Greiver M, Williamson T, Bennett TL, et al. Developing a method to estimate practice denominators for a national Canadian electronic medical record database. *Fam Pract* 2013;30(3):347-54. doi: 10.1093/fampra/cms083 [published Online First: 2013/01/12]

22. Bartholomeeusen S, Kim CY, Mertens R, et al. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22(4):442-7. doi: 10.1093/fampra/cmi054 [published Online First: 2005/06/21]

23. Knottnerus JA, Metsemakers J, Hoppener P, et al. Chronic illness in the community and the concept of 'social prevalence'. *Fam Pract* 1992;9(1):15-21. [published Online First: 1992/03/01]

24. Truyens C, Elli S, Goderis G, et al. [Dutch: 20 year General Practice in Flanders (1994-2013)]. Leuven: Acco, 2015. ISBN978-94-6292-129-0.

25. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. [published Online First: 2000/01/29]

26. Rea F, Pagan E, Compagnoni M, et al. Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies. *Epidemiology Biostatistics and Public Health* 2017;14(3):e12616:1-8.

27. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;28(29):3670-82. doi: 10.1002/sim.3733 [published Online First: 2009/10/27]

28. Alan A. Categorical data analysis. 2nd ed: Wiley 2002.

29. Nivel database for primary care morbidity registration in the Netherlands. 2019 https://www.nivel.nl/nl/

30. Osteoarthritis in general practice: data and perspectives. 2013 www.arthritisresearchuk.org

31. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763 [published Online First: 2014/02/21]

32. Tuominen U, Blom M, Hirvonen J, et al. The effect of co-morbidities on health-related quality of life in patients placed on the waiting list for total joint replacement. *Health Qual Life Outcomes* 2007;5:16. doi: 10.1186/1477-7525-5-16 [published Online First: 2007/03/17]

33. Reeuwijk KG, de Rooij M, van Dijk GM, et al. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? *Clin Rheumatol* 2010;29(7):739-47. doi: 10.1007/s10067-010-1392-8 [published Online First: 2010/02/24]

34. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;47(6):805-13. doi: 10.1016/j.semarthrit.2017.10.016 [published Online First: 2017/11/22]

35. Verkleij SP, Luijsterburg PA, Willemsen SP, et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. *Br J Gen Pract* 2015;65(637):e530-7. doi: 10.3399/bjgp15X686101 [published Online First: 2015/07/28]

36. Conaghan PG. NSAIDs or paracetamol for short-term treatment of mild to moderate knee pain in early osteoarthritis: are they equivalent? *Evid Based Med* 2016;21(1):14. doi: 10.1136/ebmed-2015-110289 [published Online First: 2015/10/21]

37. Alpert JM, Krist AH, Aycock RA, et al. Designing User-Centric Patient Portals: Clinician and Patients' Uses and Gratifications. *Telemed J E Health* 2017;23(3):248-53. doi: 10.1089/tmj.2016.0096 [published Online First: 2016/06/23]

Footnotes

Contributors: PM and DS performed the analyses, and DS, PV, RH, MS, FL, BV wrote the manuscript. DS, MS and BV are responsible for the study concept, design, the recruitment of subjects and acquisition of data. All authors participated in the interpretation of the data. All authors approved the final version of the manuscript.

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Disclaimer: The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript

Competing interests: None declared.

Ethics approval: The Intego project was presented to the Belgian Privacy Commission (no SCSZG/13/079) and approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723).

Data sharing statement: All authors had full access to all data (including statistical reports and tables) in the study and assume responsibility for the integrity of the data and the accuracy of the data analyses.

Availability of data and materials: The dataset supporting the conclusions of this article is held at the University of Leuven, Belgium, and can be shared upon contacting the corresponding author.

Figure legends

1. Figure 1. The standardized and non-standardized prevalence of patients with knee osteoarthritis by age cohorts in the Intego registry (1996-2015).
2. Figure 2. An overview of the observed and modeled trends in prevalence for men and women in the Intego registry (1996-2015). Observed (bullets) and modeled (trend line) age-standardized average annual percentage change (AAPC) in prevalence with 95% confidence intervals for time trends for patients with knee osteoarthritis in Intego register, 1996–2015. The AAPC is significantly different from zero at alpha = 0.05**.**
3. Figure 3. The standardized and non-standardized incidence of patients with knee osteoarthritis in the Intego registry (1996-2015).

Supplementary file list

1. Supplementary file 1. ICPC codes and description of codes for the disease count.
2. Supplementary file 2. ACT coding for pharmacological agents used in the management of knee osteoarthritis.
3. Supplementary file 3. Demographic characteristics of patients with knee osteoarthritis in Intego registry (1996-2015).
4. The Record checklist.

Table 1. Demographic characteristics and long-term trends in prevalence and incidence of patients with knee osteoarthritis in Intego registry (1996-2015).

	Year 1996*	**Year 2015***	**Overall trend*****	**Trend 1**		**Trend 2**		**Trend 3**	
	%	**%**	AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Prevalence									
Total	1.99	3.56	**2.5 [2.2;2.9]**	1996-2015	**2.5 [2.2;2.9]**				
Men	1.32	2.59	**3.1 [2.7;3.5]**	1996-2015	**3.1 [2.7;3.5]**				
Women	2.64	4.55	**2.4 [2.0;2.7]**	1996-2015	**2.4 [2.0;2.7]**				
Prevalence by age group**									
25-34	0.68	1.82	**4.7 [3.7;5.6]**	1996-2007	**7.7 [6.4;9.1]**	2007-2015	0.6 [-0.9;2.1]		
35-44	0.70	2.21	**5.5 [4.3;6.7]**	1996-2011	**4.5 [3.6;5.4]**	2011-2015	**9.5 [4.3;15.0]**		
45-54	1.55	3.14	**4.0 [3.3;4.8]**	1996-2011	**3.4 [2.8;4.0]**	2011-2015	**6.5 [3.2;10.0]**		
55-64	2.96	5.60	**3.0 [2.6;3.4]**	1996-2015	**3.0 [2.6;3.4]**				
65-74	6.08	8.97	**1.7 [1.3;2.2]**	1996-2015	**1.7 [1.3;2.2]**				
75-84	7.80	13.9	**2.6 [2.0;3.2]**	1996-2007	**3.6 [2.7;4.5]**	2007-2015	**1.2 [0.2;2.1]**		
≥ 85	6.27	15.0	**3.0 [2.4;3.5]**	1996-2015	**3.0 [2.4;3.5]**				
Incidence									
Total	0.42	0.38	-0.5 [-1.4;0.5]	1996-2006	**-2.6 [-4.0;-1.1]**	2006-2015	**1.9 [0.4;3.5]**		
Men	0.27	0.26	-0.2 [-1.4;1.1]	1996-2006	**-2.5 [-4.4;-0.5]**	2006-2015	**2.5 [0.5;4.5]**		
Women	0.58	0.49	-0.5 [-2.4;1.4]	1996-1999	**-8.7 [-16.2;-0.6]**	1999-2013	-0.4 [-1.2;0.5]	2013-2015	11.8 [-3.3;29.3]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval

* These percentages are standardized for the total Flemish population.

** Standardization was possible for the total population, but not for specific age cohorts.

*** Joinpoint regression modelling was used to estimate (A)APC in prevalence and incidence trends. Three possible trends were calculated during the 20-year study period.

Statistically significant differences for (A)APC are indicated in bold.

Table 2. Trends in comorbidities for patients with knee osteoarthritis (1996-2015)

Variables	1996-2000		2001-2005		2006-2010		2011-2015*		p-value **
Mean age (± SD)	55.3	(21.9)	57.6	(20.5)	57.8	(19.8)	56.9	(19.8)	0.384
Women, n (%)	972	(65%)	1234	(65%)	1419	(64%)	1412	(62%)	0.05224
Incidence, n	1503		1912		2202		2288		
Comorbidities, n (%)									
Hypertension	359	(24%)	485	(25%)	623	(28%)	593	(26%)	0.0756
Diabetes	93	(6%)	161	(8%)	252	(11%)	346	(15%)	<0.001
CV events	323	(21%)	480	(25%)	597	(27%)	614	(27%)	<0.001
GI complication (ulcer)	28	(2%)	60	(3%)	59	(3%)	61	(3%)	0.3585
Renal failure	23	(2%)	70	(4%)	71	(3%)	66	(3%)	0.1025
Depression	141	(9%)	230	(12%)	259	(12%)	287	(13%)	0.009
Obesity	74	(5%)	101	(5%)	145	(7%)	191	(8%)	<0.001
Osteoporosis	57	(4%)	81	(4%)	107	(5%)	103	(5%)	0.2303
Cancer	29	(2%)	60	(3%)	59	(3%)	61	(3%)	<0.001
Asthma	125	(8%)	205	(11%)	328	(15%)	392	(17%)	<0.001
Substance abuse	4	(0%)	22	(1%)	31	(1%)	48	(2%)	<0.001
Disease burden, n	1.6267		1.8383		2.1848		2.3387		<0.001

Legend:

*** four time intervals of five years were defined to evaluate trends for incident patients with knee osteoarthritis.**

**** *p*-value for the comorbidities was calculated with the Cochran-Armitage trend test; p-value for age was calculated with the Jonckheere-Terpstra trend test.**

Table 3. Medication use in patients with knee osteoarthritis in Intego registry (1996-2015).

Group/ Medication	Prev. in 1996	Prev. in 2015	Summary	Trend 1		Trend 2		Trend 3	
			AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Acetaminophen	5.3	19.2	**6.7 [5.6-7.7]**	1996-2010	**8.0 [6.8-9.2]**	2010-2015	**3.1 [0.3;5.9]**		
Males	5.2	17.4	**5.8 [4.9-6.6]**						
Females	5.4	20.2	**7.0 [5.8-8.3]**	1996-2010	**8.7 [7.3;10.1]**	2010-2015	2.7 [-0.6;6.0]		
Oral NSAID (exclusion cox-2)	28.4	29.4	0.0 [-1.1;1.1]	1996-2002	-1.0 [-3.5;1.6]	2002-2008	2.4 [-0.1;5.0]	2008-2015	-1.2 [-2.4;0.1]
Males	28.6	28.8	0.5 [-0.2;1.2]	1996-2009	**1.1 [0.4;1.9]**	2009-2015	0.5 [-0.2;1.2]		
Females	28.3	29.6	0.3 [-0.1;0.8]						
Cox-2 selective NSAID	3.0	2.3	-7.7 [-36.0; 33.0]	2000-2004	-2.7 [-29.3;33.9]	2004-2007	-48.4 [-93.5; 309.5]	2007-2015	11.8 [-3.4;29.5]
Males	2.2	1.8	**-13.3 [-19.3;-6.7]**						
Females	3.4	2.7	-7.3 [-34.0;30.1]	2000-2004	-3.3 [-29.1;32.0]	2004-2007	-47.2 [-92.2; 257.6]	2007-2015	12.0 [-2.9;29.2]
Topical NSAID	7.8	5.9	-1.0 [-2.4; 0.4]	1996-2003	**-4.7 [-8.1;-1.2]**	2003-2015	1.2 [-0.0;2.4]		
Males	9.3	5.8	-0.9 [-2.2;0.5]						
Females	7.1	5.9	-0.8 [-2.3;0.7]	1996-2003	**-4.3 [-8.0;-0.4]**	2003-2015	1.3 [-0.0;2.6]		
Weak opioids	2.8	6.1	**4.0 [0.9;7.3]**	1996-1998	**36.3 [0.4;85.2]**	1998-2009	-0.9 [-2.3;0.5]	2009-2015	**4.0 [1.6;6.4]**
Males	1.5	5.2	**2.9 [1.5;4.4]**						
Females	3.3	6.7	2.8 [-0.0;5.7]	1996-2000	**14.7 [1.6;29.4]**	2000-2008	-3.2 [-6.4;0.2]	2008-2015	**3.5 [0.6;6.4]**
Strong opioids	2.5	4.3	1.9 [-0.4;4.3]	1996-2003	**9.0 [2.5;16.0]**	2003-2015	**-2.0 [-3.7;-0.3]**		
Males	1.7	3.6	-0.2 [-2.0; 1.6]						
Females	2.9	4.7	**2.3 [0.3;4.3]**	1996-2003	**10.0 [4.4;15.9]**	2003-2015	**-2.0 [-3.4;-0.5]**		
Parenteral glucocorticoids	9.1	8.1	-0.7 [-1.8;0.5]	1996-2005	**-2.1 [-3.5;-0.7]**	2005-2012	**2.7 [0.8;4.7]**	2012-2015	-4.1 [-9.2;1.2]
Males	8.1	8.6	**0.8 [0.0;1.6]**						
Females	9.6	7.9	**-1.3 [-2.6; 0.0]**	1996-2003	**-3.8 [-6.0;-1.5]**	2003-2012	**2.0 [0.6;3.4]**	2012-2015	-5.1 [-10.7;0.8]
Glucosamine*	0.6	1.8	**8.6 [2.4;15.1]**	2001-2004	**64.1 [25.0;115.3]**	2004-2011	**-9.6 [-14.3;-4.4]**	2011-2015	9.8 [-0.6:21.2]
Males	0.1	1.8	17.3 [-18.8; 69.5]	2001-2003	212.4 [-83.1;5664.3]	2003-2015	-0.4 [-4.8;4.2]		
Females	0.9	1.8	**6.8 [0.4;13.7]**	2001-2004	**56.7 [18.3;107.5]**	2004-2011	**-10.0 [-15.3;-4.3]**	2011-2015	8.2 [-3.6;21.4]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval; Prev., prevalence

***glucosamine: registration starts from 2001; cox-2 selective NSAID starts from 2000**

Bold: indicates that the (A)APC is significantly different from zero at the alpha= 0.05 level

¥= three possible time trends were computed with the joinpoint regression analysis. The corresponding time cohorts and APC are mentioned in these three columns

Figure 1.

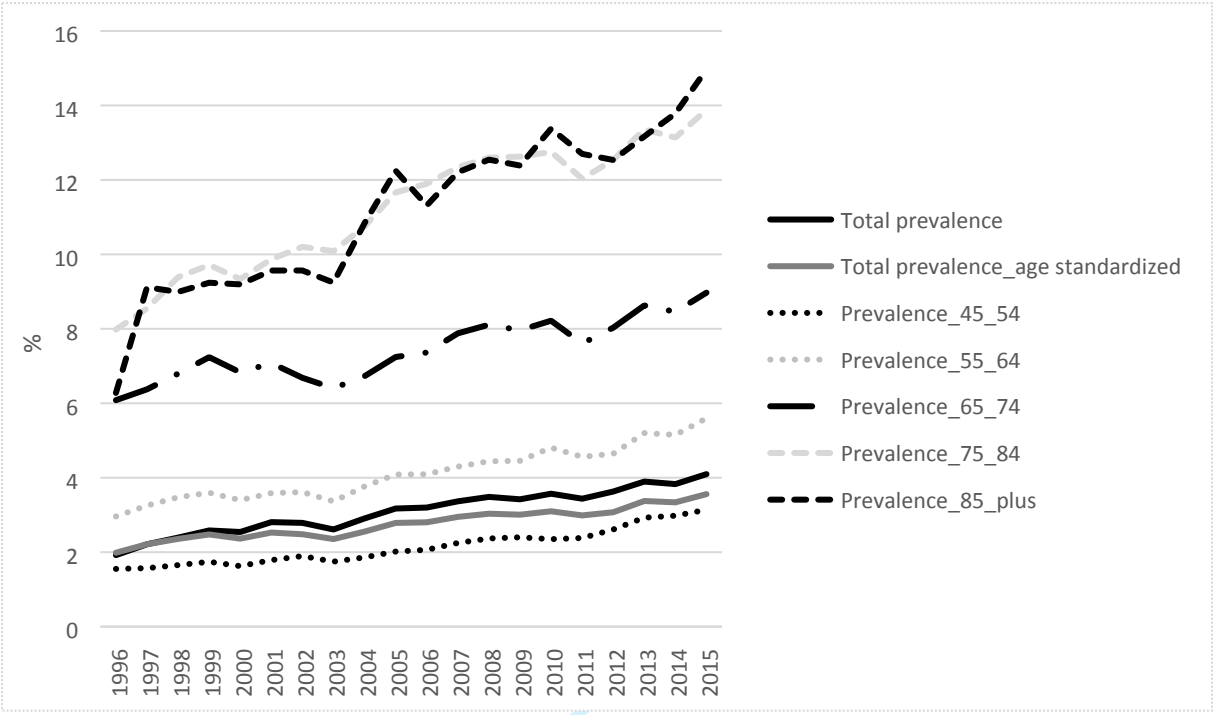


Figure 2.

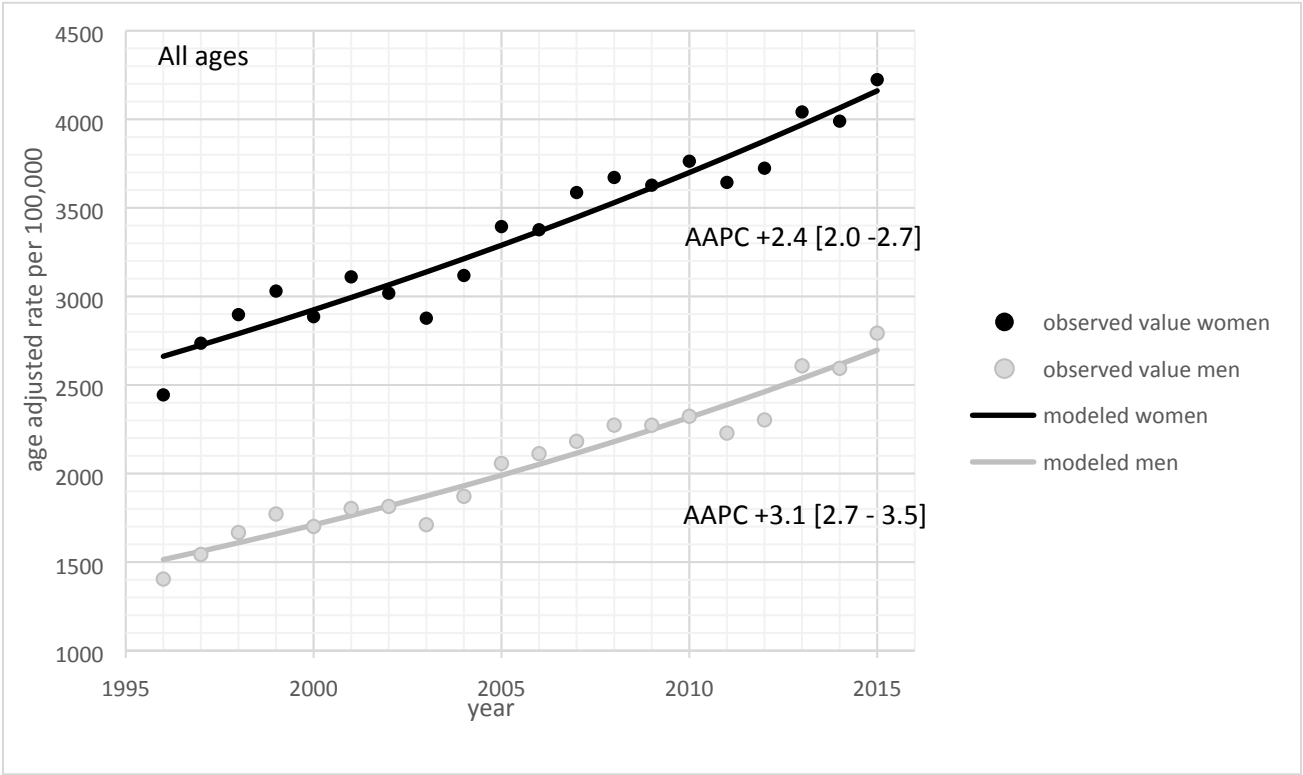
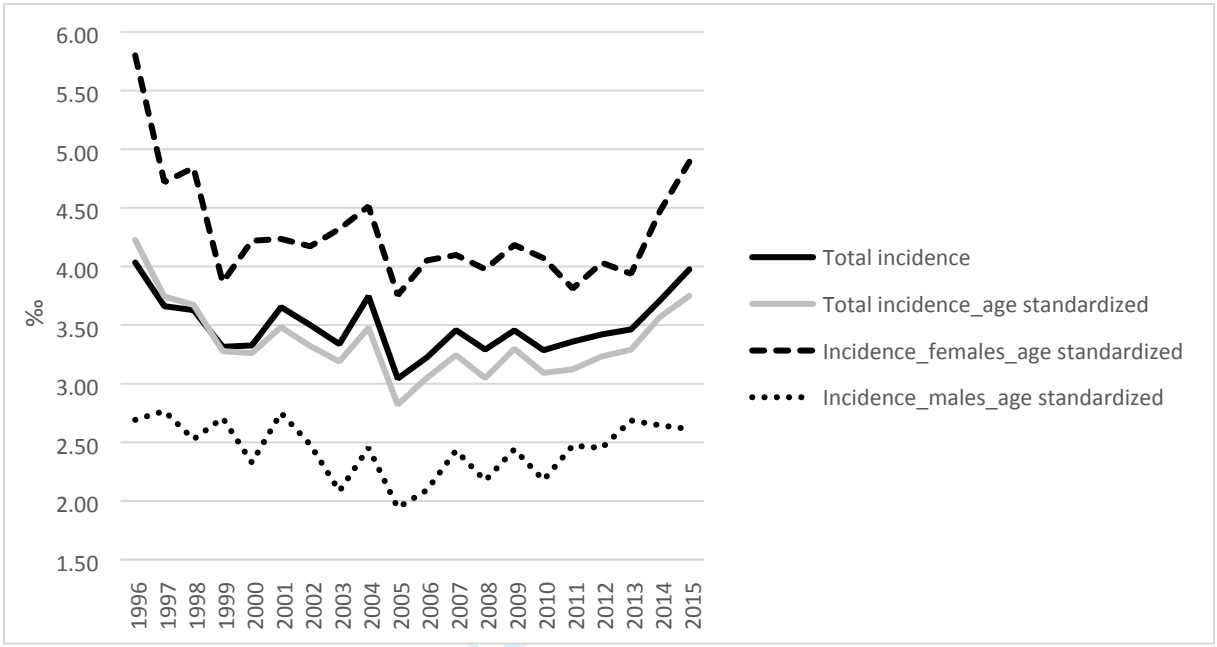


Figure 3.



SUPPLEMENT 1. ICPC codes and description of codes for the disease count

Codes to measure the disease count

The combination of the following 92 ICPC-2 codes were used to measure the disease count. If codes are not mutually exclusive (e.g. T89 and T90), then they count for one.

ICPC code	Description
A79	Malignancy NOS
A90	Congenital anomaly OS/multiple
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B78	Hereditary haemolytic anaemia
B83	Purpura/coagulation defect
B90	HIV-infection/aids
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
F83	Retinopathy
F84	Macular degeneration
F94	Blindness
H83	Otosclerosis
H84	Presbyacusis
H86	Deafness
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K82	Pulmonary heart disease
K86	Hypertension uncomplicated
K87	Hypertension complicated
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L88	Reumatoãde arthritis
L89	Osteoarthrosis of hip
L90	Osteoarthrosis of knee
L91	Osteoarthrosis other
L95	Osteoporosis
L98	Acquired deformity of limb
N70	Poliomyelitis
N74	Malignant neoplasm nervous system
N85	Congenital anomaly neurological

N86	Multiple sclerosis
N87	Parkinsonism
N88	Epilepsy
N89	Migraine
N90	Cluster headache
N92	Trigeminal neuralgia
P15	Substance abuse: chronic alcohol
P28	Limited function/disability (p)
P70	Dementia
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P77	Suicide/suicide attempt
P79	Phobia/compulsive disorder
P80	Personality disorder
P85	Mental retardation
P98	Psychosis NOS/other
R79	Chronic bronchitis
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R95	Chronic obstructive pulmonary disease
R96	Asthma
S77	Malignant neoplasm of skin
S87	Dermatitis/atopic eczema
S91	Psoriasis
S97	Chronic ulcer skin
T71	Malignant neoplasm thyroid
T80	Congenital anom endocrine/metab.
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U04	Incontinence urine
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
W72	Malignant neoplasm relate to preg.
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malign neoplasm male genital other
Y85	Benign prostatic hypertrophy

Other ICPC codes used in this manuscript

ICPC code	description
P17	Substance abuse: tobacco
P19	Substance abuse: drug abuse
L89	Osteoarthritis of the hip
L90	Osteoarthritis of the knee
L91	Osteoarthritis of other locations (other than knee/hip)

ICPC codes used with Intego software to define comorbidity

Definition of cancer

Intego uses a set of 22 ICPC-2 codes to define cancer as a comorbidity: A79, B73, B72, B74, D74, D75, D76, D77, L71, N74, R84, R85, T71, U75, U76, U77, W72, X75, X76, X77, Y77, and Y78.

Definition of substance abuse

Intego uses a combination of three ICPC-2 codes to define substance abuse: P15, P 17, and P19.

Supplement 2. ACT coding for pharmacological agents used in the management of knee osteoarthritis.

	ACT coding
Acetominophen	N02BE01
Oral NSAID (exclusion cox-2 selective)	M01AB M01AC-M01AE M01AG
COX-2 selective NSAID	M01AH
Topical NSAID	M02AA
Glucosamine supplements	M01AX05
Chondroitin supplements	M01AX25
Hyaluronic acid	M09AX01
Weak opioids	N02AX02 N02AJ01 N02AJ02 N02AJ03 N02AJ06 N02AJ07 N02AJ08 N02AJ09 N02AJ13 N02AJ14 N02AJ15
Strong opioids	N02AA N02AB N02AC N02AD N02AE N02AF
Glucocorticoids	H02AB

Supplement 3. Demographic characteristics of patients with knee osteoarthritis in Intego registry (1996-2015).

	1996***		2005		2015	
	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized
Prevalence, gender						
Total	1.595/83011	1.92; 1.99	4069/128251	3.17;2.79	5049/123261	4.09; 3.56
Men	518/39648	1.31; 1.32	1348/61446	2.20;1.97	1817/58841	3.09; 2.59
Women	1077/43363	2.48; 2.64	2721/66805	4.07;3.67	3232/64420	5.02;4.55
Prevalence, age cohorts**						
25-34	101	0.68	272	1.55	324	1.82
35-44	98	0.70	225	1.18	353	2.22
45-54	155	1.55	372	2.01	532	3.13
55-64	240	2.96	606	4.08	863	5.60
65-74	442	6.08	887	7.24	1002	9.00
75-84	303	7.98	1038	11.66	1130	13.9
≥ 85	84	6.28	362	12.24	613	15.0
Incidence, gender						
Total	325/81416	0.40; 0.42	378/124182	0.30;0.28	470/118212	0.40; 0.38
Men	102/39130	0.26; 0.27	129/60098	0.21;0.19	167/57024	0.29; 0.26
Women	223/42286	0.53; 0.58	249/64084	0.39;0.38	303/61188	0.50;0.49

Legend:

N=yearly contact group: the number of patients that visited their general practitioner at least once during once year

***the first % refers to the age-specific data from the Intego register; the second % is the standardized Intego data for the total Flemish population.**

** Standardization was possible for the total population, but not for specific age cohorts.**

*** Data are available for 20-year period. In this table 10-year interval periods are described.**

The RECORD statement

Checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Title (Title page and abstract) 1.2 Geographic region: abstract 1.3 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, p.2, paragraph 1-4
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, p.2, paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, p. 3, design

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods, pp. 3-4, design and data collection
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1 Methods, p. 3, appendix A for ICPC codes and appendix B for ACT codes 6.2 Intego registry external validation described in Truyers et al. Reference 6.3 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1 Methods, p. 3, design, appendix A and appendix B
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Page 5: Methods, design pp. 3-4, the Intego

		Describe comparability of assessment methods if there is more than one group			Database is explained in detail
Bias	9	Describe any efforts to address potential sources of bias			Methods, design, p.3 and Discussion, pp. 11-12, paragraph 5
Study size	10	Explain how the study size was arrived at			NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods, data analysis p.5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			(a) methods, data analysis p.5 (b) NA (c) NA (d) NA (e) NA
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the	12.1 Data sharing statement, p.14

				investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2 Availability of data and materials, p.14
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	NA
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Results, pp. 6-9 Table 1 Figures 1-3 (b) NA (c) NA

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			(a) Results, pp. 6-9 Table 1-3 Figures 1-3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			NA
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion, last paragraph with conclusions p.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Discussion, paragraph 5, pp. 11-12

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, pp. 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, pp. 10-12
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Funding, p.14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials, p.14

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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The epidemiology of knee osteoarthritis in general practice: a registry-based study

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Abstract

Objectives The present study investigated (i) trends in the prevalence and incidence of knee osteoarthritis over a 20-year period; (ii) trends in multimorbidity; and (iii) trends in drug prescriptions.

Design Registry-based study.

Setting Primary health care, Flanders, Belgium.

Participants Data were collected from Intego, a general practice-based morbidity registration network. In the study period between 1996 and 2015 data from 440,140 unique patients were available.

Outcome measures Trends in prevalence and incidence rate of knee osteoarthritis were computed using joinpoint regression analysis. The mean disease count was calculated to assess trends in multimorbidity. In addition, the number of drug prescriptions was identified by the Anatomical Therapeutic Chemical Classification code and trends were equally recorded with joinpoint regression.

Results The prevalence of knee osteoarthritis increased from 1.99% in 1996 to 3.56% in 2015. An upward trend was observed with an average annual percentage change (AAPC) of 2.5 (95%CI 2.2-2.9). The incidence remained stable with 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5). The mean disease count significantly increased from 1.63 to 2.34 ($p<0.001$) for incident cases with knee osteoarthritis. Finally, we observed a significantly positive trend in the overall prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1).

Conclusions Increased prevalence, multimorbidity, and number of drug prescriptions confirm an increased burden of knee osteoarthritis. In future, these trends can be used to prioritize initiatives for improvement in care.

Key Words

Knee osteoarthritis; multimorbdity; general practice; trends; burden of illness

Article Summary

Strengths and limitations of this study

- The Intego open registry provides real-world data of 440,140 unique patients in a primary care setting, representative for the Flemish population.
- This registry database, with data over a 20-year time period (1996-2015), lends itself perfectly for trend analyses.
- Estimates on the prevalence and incidence of knee osteoarthritis are scarce for primary care settings. This study defines knee osteoarthritis when it becomes a healthcare problem for the patient.
- Data completeness depends on the quality of registration of the participating general practitioners. To this end, only optimal registration practices are included in the Intego database.
- The lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes.

Introduction

Osteoarthritis (OA) is the most common joint disease and is expected to become the fourth leading cause of disability worldwide by 2020.[1] OA mainly affects the joints of the knees, hips, hands, facets and feet, but knee OA accounts for 83% of the total OA burden.[2] The prevalence of knee OA varies according to the definition: from subjective (population-based) assessments to clinical and radiographic definitions, often with low levels of concordance between them.[3] However, estimates on the prevalence of knee OA are scarce for primary care settings.[4]

At present, the purposes of conservative knee OA treatment are to alleviate pain, to improve the function of the joint and to slow down joint damage by pharmacological and non-pharmacological means.[5] All patients should be offered the following core conservative interventions: information to enhance their understanding about OA, advice to exercise, and to achieve weight loss for people who are obese or overweight.[6 7] Pharmacological management is dominated both by acetaminophen and by nonsteroidal anti-inflammatory drugs (NSAIDs).[5 8 9] The presence of multimorbidity may also affect choices in the pharmacological management, since multimorbidity and polypharmacy are closely related.[6 10 11] Almost all patients with OA suffer from at least one comorbid disease.[12] Common comorbidities in patients with knee OA are cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and obesity.[13] Nevertheless, multimorbidity-adapted management protocols are being developed and provide tailored guidance for pharmacological management and exercise therapy.[5 7] Numerous reports indicate that the number of people suffering from chronic diseases, multimorbidity and polypharmacy continues to increase, but those studies are mainly based on cross-sectional studies in different populations.[14] Time trends in the prevalence of multimorbidity and polypharmacy are scare.[15 16] The

Flemish primary care-based Intego database offers an excellent opportunity to extract "real world" data and evaluate time trends.[17]

The aims of the present study were 1) to evaluate time trends in the prevalence and incidence of patients with knee OA managed in general practice; 2) to assess trends in the disease burden and 3) to assess trends in GPs' drug prescriptions over a 20-year period.

Methods

Data source

This trend analysis study was performed using Intego, a general practice-based morbidity registration network in Flanders, Belgium.[17] The Intego database comprises extracted information from electronic health records (EHR) of general practitioners (GPs), all using the medical software programme Medidoc (Corilus NV, Aalter, Belgium).[18] Systematic collection of data started in 1994. In 2015, 111 GPs of 48 practices evenly spread throughout Flanders, collaborated in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The selection procedure was described in detail previously.[17] The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results, some background information (including gender and year of birth) and some biomedical parameters (i.e. blood pressure, height, weight, smoking status and mortality), using computer-generated keywords internally linked to codes. With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus and automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[19] Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.[20]

Study population

For the present study, data over a 20-year time interval from 1 January 1996 to 31 December 2015 were used. In this period, 440,140 unique patients were registered in the Intego database. The yearly contact group (=YCG) is defined as the number of different patients who consulted their GP in a given year.[21] During the study period, the YCG varied between 81,763 and 151,971 people (see supplementary file 1 for the exact number per year). Throughout the study period, 79 GP practices provided their data, with 72% contributing for 15 or more years (see supplementary file 2). This study was reported in accordance with the RECORD checklist specific to observational studies using routinely collected health data.[22]

Measures

Data on prevalence and incidence

Patients with knee OA were identified based on an ICPC-2 coded diagnosis in their EHR. The prevalence of a population is the proportion of the population with the disease at a specified time. Unlike incidence rates, which focus on new events, prevalence focuses on existing states. Because of the design of Intego (no episode registration and no recording of cure), prevalence rates could only be calculated on incurable chronic diseases, such as knee OA.[17] The incidence in Intego is calculated as the number of new cases of disease divided by the person-time magnitude. Calculating disease prevalence and incidence requires both a numerator (number of events or persons with a disease) and a matching denominator (the 'population at risk' being studied). Determining primary care practice denominators is challenging.[23] In this study, the YCG was used as denominator for all time trend analyses.[21]

Data on multimorbidity

Patients' medical history before they presented with knee OA was registered for all cases between 1996 and 2015. There are several instruments available to calculate multimorbidity, for example, the Carlson Index, the Cumulative Illness Rating Scale, the Index of Coexistent Diseases and the Kaplan Index.[24-27] For this study, the disease burden was calculated for all incident cases with knee OA. For this disease count, a list of chronic diseases based on the paper by Knottnerus et al was used.[28] For the presence of chronic kidney disease (CKD), the glomerular filtration rate (GFR) was based on the closest creatinine measurement in the two years before or after presentation with knee OA diagnosis (Supplementary file 3: ICPC codes for diagnosis and multimorbidity).

Data on drug prescriptions

The prescription of medication for knee OA, including acetaminophen, oral and topical anti-inflammatory drugs, cox-2 selective anti-inflammatory drugs, weak and strong opioids, parenteral glucocorticoids, parenteral hyaluronic acid and glucosamine was extracted from Intego for all prevalent cases with knee OA (Supplementary file 4: used ACT codes). Prescription of medication was considered positive if it was prescribed at least once a year.

Statistical analysis

Descriptive statistics, with frequency distribution and percentages, were used to measure the prevalence (/100 patients) and incidence (/1000 patient years at risk) of patients with knee OA. Data were stratified by gender and ten-year age cohorts, starting from 25 with 85 years and older as the last cohort. The rates were age-standardized by taking the Flemish population of the year 1996 as reference population.[29] Additionally, possible time trends were analysed in the age-standardized cohorts with joinpoint regression analysis.[30] Joinpoint analysis identifies the best-fitting point, where a statistically significant change (called the "joinpoint") occurs, and determines the trends between joinpoints. Joinpoint regression allows us to identify the time point(s) of follow-up at which trends significantly change.[31] A

minimum number of three observations from a joinpoint to either end of the data, and a minimum number of four observations between two joinpoints were required.[32] The annual percentage change (APC) is proposed to summarize and compare the rates of changes between successive change points.[33] In the final model, the joinpoint analysis also provides an average annual percentage change (AAPC) as an average of APC estimates.[33] This means that trends over a specific period were described by the annual percent change (APC), while trends over the whole 1996–2015 period were summarised using the average annual percent change (AAPC). Analysis was performed with the Joinpoint Regression Program (version 3.5.3, released in May 2013 and available at http://surveillance.cancer.gov/joinpoint). This program starts with the minimum number of joinpoint (e.g. zero joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model. This enables the user to test that an apparent change in trend is statistically significant.

Trends in the multimorbidity profile for incident cases with knee OA were explored over four time intervals of five years (1996-2000, 2001-2005, 2006-2010 and 2011-2015) by the Cochran-Armitage test and the Jonckheere-Terpstra test. The Cochran-Armitage test for trend analysis is a modified Pearson's chi-square test to assess the association between binary and ordinal categories (e.g. between comorbidities and time intervals). The Jonckheere-Terpstra trend test was used to analyse trends for continuous variables (e.g. between age and time intervals).[34]

Over the same 20-year time period, trends in drug prescriptions for prevalent cases with knee OA were analyzed using joinpoint regression analysis, as described above. Two-sided p-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using R Software Version 3.3.2 (Free Software Foundation Inc., Boston, MA, USA).

Patient involvement

No patients were involved in defining the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of the results.

Results

Demographic characteristics and trends in the prevalence and incidence of patients with knee osteoarthritis (1996-2015)

Between 1 January 1996 and 31 December 2015, the Intego database included data on 440,140 unique patients. Table 1 shows the demographic characteristics of the patients with knee OA by gender and age cohorts in Table 1.The age-standardized prevalence of knee OA increased by 79% from 1.99% in 1996 to 3.56% in 2015 (AAPC= 2.5, 95%CI 2.2-2.9, Figure 1 and supplementary file 5). Woman have a higher prevalence than men do, but over the 20 years of the study men have a higher relative increase in prevalence (AAPC= 3.1, 95%CI 2.7-3.5 for men versus AAPC= 2.4, 95%CI 2.0-2.7 for women).

Figure 2 presents the observed and modeled long-term time trends in prevalence by gender. The age-standardized incidence of patients with knee OA remained stable with 4.23‰ in 1996 and 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5), but showed a positive trend between 2006 and 2015 from 3.05‰ to 3.75‰, respectively (APC= 1.9, 95%CI 0.4-3.5) (Figure 3). Between 2006 and 2015, this positive trend was higher for men (APC= 2.5, 95%CI 0.5-4.5) than for women (APC= 1.9, 95%CI 0.4-3.5) (Figure 3).

Trends in multimorbidity in newly diagnosed patients with knee osteoarthritis (1996-2015)

In the 20-year study period, the mean age at diagnosis of knee OA remained stable (p=0.384) with 55.3 years in 1996 and 56.9 years in 2015, respectively, while a non-significant decline was found in the proportion of women in this period (65% to 62%, p=0.052). Additionally, the disease burden was defined by calculating the mean disease count of patients with knee OA.[28] This mean disease count showed a significant increase in the study period ranging from 1.6 to 2.3 (p<0.001), meaning that the comorbid burden of patients with knee OA increased. In this study, the following comorbidities increased significantly: the proportions of patients with diabetes (6% to 15%, p<0.001), cardiovascular events (21% to 27%, p<0.001), depression (9% to 13%, p=0.009) and obesity (5% to 8%, p<0.001). Hypertension, gastro-intestinal ulcer and renal failure remained stable. Additionally, we noted that the proportion of knee OA patients with cancer (2% to 3%, p<0.001), asthma (8% to 17%, p<0.001) and substance abuse (0% to 2%, p<0.001) increased significantly during the study period, while the proportion with osteoporosis remained stable (Table 2).

Trends in prescriptions for patients with knee osteoarthritis (1996-2015)

The prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1) for patients with knee OA increased during the study period (Table 3). The prevalence of patients with knee OA who were prescribed acetaminophen was lower than those with oral NSAIDs (19.2% versus 29.4% in 2015; 5.3% versus 28.4% in 1996). The prescription of oral, topical and cox-2 selective NSAIDs remained stable for both genders during the study period. The use of strong opioids showed a strong increase between 1996 and 2003 (AAPC= 9.0, 95%CI 2.5-16), but then decreased slightly in the period from 2003 to 2015 (AAPC= -2.0, 95%CI 3.7 to -0.3).

Discussion

This study presents estimates of knee OA prevalence and incidence based on a large morbidity registration network for general practice in Belgium. During the 20-year study period, the age-standardized prevalence of knee OA significantly increased while the age-standardized incidence rate remained stable. During the study period, patients with knee OA experienced higher multimorbidity, as

shown by almost a doubling of the disease count. Oral NSAIDs were most frequently prescribed for the prevalent patients with knee OA, while prescription of acetaminophen, weak opioids and glucosamine showed an overall positive trend.

This study shows that the prevalence rate of knee OA significantly increased even after standardization of the study population. General practice morbidity registration networks in other European countries show similar rates for knee OA: in the Netherlands, an overall prevalence of 3.4% and incidence of 3.2‰ was registered in 2016.[35] In our study, we found similar rates with 3.56% and 3.75‰ respectively for the year 2015. In the UK, the estimated proportion of people who sought treatment for knee OA is high: 18% of the population aged 45 and over consulted their GP for knee OA.[36] In our study, we found a consultation prevalence of 21% for the same reference year (2010) and age cohorts. The latter study also found that OA is the most common musculoskeletal condition in older people and that just over half of all patients consulting their GP about OA have knee OA. In the near future, the number of people with knee OA is expected to rise considerably because of an aging population and obesity trends.[37] Nevertheless, the increasing prevalence of knee OA in general practice registration could also be attributed to other factors, for example: better access to general practice, more awareness of the public of preventive medicine, better diagnostics, better registration and higher demands and expectations of older people to remain physically active. Future qualitative research with different stakeholders could assess these possible explanations.

Osteoarthritis is one of the diseases with the highest rate of multimorbidity, with reported rates of 68% to 85%.[12 38] If patients with comorbid conditions need replacement surgery, they tend to have a higher risk of revisions and long-term mortality.[39]. Coexisting disorders may worse pain and bring additional impairments, which necessitate adaptations to the conservative management of knee OA.[13 40] In our study, knee OA was also strongly associated with the following comorbidities: asthma, cancer, depression and substance abuse. The substantial contribution of OA to multimorbidity and frailty should be recognized, further investigated, and needs extra attention in general practice management of long-term conditions.

Pharmacological management of knee OA in general practice is dominated both by acetaminophen and by NSAIDs, as they are both recommended in evidence-based guidelines.[5 7-9] Although the review by Machado et al. suggested that acetaminophen has little clinical benefit in OA, guidelines recommend starting with acetaminophen, because the adverse side effect profile of NSAIDs.[41] In our study, NSAIDs were the most frequently prescribed pain drug for prevalent patients with knee OA. Verkleij et al. observed the effects of medication on 104 patients with knee OA in general practice. They demonstrated no significant difference regarding knee pain and knee function between patients taking diclofenac or acetaminophen.[42] Furthermore, the discrepancy between drug prescription by the professional and drug use by the patient can be accumulated by the over the counter availability of acetaminophen and some

low oral NSAID in Belgium. Over the counter availability, could be considered as part of self-care to reduce the burden on health care systems and increase people's choice to take informed treatment decisions, but the medical outcome resulting from therapeutic options bypassing the physician prescription stays a major issue.[43] In Intego we look at the GP's prescription and not the actual drug use by the patient. If acetaminophen should remain the ''first-line' pharmacological treatment for patients with a new episode, the effects of acetaminophen and the role in patients with multimorbidity should be further investigated.[44]

Strengths and limitations

The major strengths of this study are the long-term follow-up data of a practice-based morbidity registration network in general practice. Intego covers more than 2% of the Flemish population, highly representative for age and gender.[17] A sufficient sample size in primary care registration networks is advised to be about 1% of the population, which allows the study of common diseases.[45] Longitudinal data in registry-based studies are used to track the natural history of diseases over time and enable us to perform time-to-event analyses. General practices have to pass three quality criteria before being accepted as participants in Intego, what results in a reliable morbidity database.[17] Important attributes of most patient registries are their large sample size and data variability.[46] A few limitations must also be considered. Lack of data verification is a common problem in registry-based studies with longitudinal data of large sample size. In Intego, the lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes with a detailed thesaurus, individual patients are followed over time and their history is taken into account. If diagnoses are not mutually exclusive, then they count for one. Secondly, we are aware that accurate coding is always a risk for possible underdiagnosis. The difference between early-onset knee OA and chronic, established knee OA can not be established with the ICPC codes. Standardized coding for OA should be adopted in general practice to accurately describe the extent of the condition and to maximize the conservative management options to improve quality of life. Furthermore, there is no obligation for patients to be registered with a particular GP in Belgium. Therefore, it can be difficult to define 'the population at risk' for epidemiological studies in general practice. In Intego, the YCG was used as denominator for all trend analyses. Importantly, mortality data are lacking in Intego. Therefore, patients in the incidence analysis are considered at risk until the diagnosis or until December 31 of any specific year to compensate for possible overestimation in this registry-based study. Finally, obesity and smoking status could not be reliably assessed from the Intego database, because of insufficient registration in the patient files. To date, information on socioeconomic status on patient level can not be extracted from Intego. Quality improvement initiatives should make GPs more aware of the necessity of properly recording up-to-date patient variables, such as BMI, in the EHR because of their growing importance in patient-tailored management strategies. Patient portals and remote access to their own medical health record are future

initiatives, where the patient could play a more central role to help the GP in keeping these parameters more up-to-date by shared responsibility.[47]

Conclusion and recommendations

In conclusion, increased prevalence, multimorbidity, and number of drug prescriptions, together with the young age at incidence, confirm the high burden of knee OA. Our registry-based study represents knee OA diagnoses at a time it becomes a health issue for patients. Professionals face more difficulties in their conservative management options due to rising multimorbidity. In future, these health trends can be used to prioritize initiatives for improvement in care.

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References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/S0140-6736(12)61689-4
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2
3. Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185-99. doi: 10.1093/bmb/lds038
4. Bedson J, Jordan K, Croft P. The prevalence and history of knee osteoarthritis in general practice: a case-control study. *Fam Pract* 2005;22(1):103-8. doi: 10.1093/fampra/cmh700 [published Online First: 2005/01/11]
5. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22(3):363-88. doi: 10.1016/j.joca.2014.01.003 [published Online First: 2014/01/28]
6. National Institute for Health and Care Excellence (NICE): Osteoarthritis: care and management (quality standard 87): http://guidance.nice.org.uk/qs87. Accessed 20 May 2018.
7. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72(7):1125-35. doi: 10.1136/annrheumdis-2012-202745 [published Online First: 2013/04/19]
8. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64(4):465-74. [published Online First: 2012/05/09]
9. Kingsbury SR, Gross HJ, Isherwood G, et al. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014;53(5):937-47. doi: 10.1093/rheumatology/ket463 [published Online First: 2014/02/04]
10. Harding PA, Holland AE, Hinman RS, et al. Physical activity perceptions and beliefs following total hip and knee arthroplasty: a qualitative study. *Physiother Theory Pract* 2015;31(2):107-13. doi: 10.3109/09593985.2014.959581 [published Online First: 2014/12/17]
11. de Rooij M, Steultjens MPM, Avezaat E, et al. Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity. *Physical Therapy Reviews* 2013;18(2):101-11. doi: 10.1179/1743288X12Y.0000000056

12. van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord* 2008;9:95. doi: 10.1186/1471-2474-9-95 [published Online First: 2008/06/28]
13. Reeuwijk KG, de Rooij M, van Dijk GM, et al. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? *Clin Rheumatol* 2010;29(7):739-47. doi: 10.1007/s10067-010-1392-8 [published Online First: 2010/02/24]
14. Freid VM, Bernstein AB, Bush MA. Multiple chronic conditions among adults aged 45 and over: trends over the past 10 years. *NCHS Data Brief* 2012(100):1-8. [published Online First: 2012/10/30]
15. van den Akker M, Vaes B, Goderis G, et al. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. *PLoS One* 2019;14(2):e0212046. doi: 10.1371/journal.pone.0212046 [published Online First: 2019/02/13]
16. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14 Suppl 1:28-32. doi: 10.1080/13814780802436093 [published Online First: 2008/10/31]
17. Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48. doi: 10.1186/1472-6947-14-48 [published Online First: 2014/06/08]
18. Vanbeselaere V, Truyers C, Elli S, et al. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. *BMC Cardiovasc Disord* 2016;16:61. doi: 10.1186/s12872-016-0235-1 [published Online First: 2016/03/30]
19. Okkes IM, Becker HW, Bernstein RM, et al. The March 2002 update of the electronic version of ICPC-2. A step forward to the use of ICD-10 as a nomenclature and a terminology for ICPC-2. *Fam Pract* 2002;19(5):543-6. [published Online First: 2002/10/03]
20. WHO Collaborating Centre for Drug Statistics Methodology: ATC/DDD Index 2010. Available at http://www.whocc.no/atc_ddd_index. Accessed February 28th, 2018.
21. Bartholomeeusen S, Kim CY, Mertens R, et al. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22(4):442-7. doi: 10.1093/fampra/cmi054 [published Online First: 2005/06/21]
22. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]
23. Greiver M, Williamson T, Bennett TL, et al. Developing a method to estimate practice denominators for a national Canadian electronic medical record database. *Fam Pract* 2013;30(3):347-54. doi: 10.1093/fampra/cms083 [published Online First: 2013/01/12]
24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. [published Online First: 1987/01/01]
25. Shah AN, Vail TP, Taylor D, et al. Comorbid illness affects hospital costs related to hip arthroplasty: quantification of health status and implications for fair reimbursement and surgeon comparisons. *J Arthroplasty* 2004;19(6):700-5. [published Online First: 2004/09/03]
26. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968;16(5):622-6. doi: 10.1111/j.1532-5415.1968.tb02103.x [published Online First: 1968/05/01]
27. Piccirillo JF, Lacy PD, Basu A, et al. Development of a new head and neck cancer-specific comorbidity index. *Arch Otolaryngol Head Neck Surg* 2002;128(10):1172-9. doi: 10.1001/archotol.128.10.1172 [published Online First: 2002/10/09]
28. Knottnerus JA, Metsemakers J, Hoppener P, et al. Chronic illness in the community and the concept of 'social prevalence'. *Fam Pract* 1992;9(1):15-21. [published Online First: 1992/03/01]

29. Truyens C, Elli S, Goderis G, et al. [Dutch: 20 year General Practice in Flanders (1994-2013)]. Leuven: Acco, 2015. ISBN978-94-6292-129-0.
30. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. [published Online First: 2000/01/29]
31. Rea F, Pagan E, Compagnoni M, et al. Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies. *Epidemiology Biostatistics and Public Health* 2017;14(3):e12616:1-8.
32. Yu B, Barrett MJ, Kim H-J, et al. Estimating joinpoints in continuous time scale for multiple change-point models. *Computational Statistics & Data Analysis* 2007;51(5):2420-27. doi: https://doi.org/10.1016/j.csda.2006.07.044
33. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;28(29):3670-82. doi: 10.1002/sim.3733 [published Online First: 2009/10/27]
34. Alan A. Categorical data analysis. 2nd ed: Wiley 2002.
35. Nivel database for primary care morbidity registration in the Netherlands. Available at https://www.nivel.nl/nl/. Accessed, May 6th, 2018.
36. Osteoarthritis in general practice: data and perspectives. 2013. Available at www.arthritisresearchuk.org. Accessed, May 23th, 2018.
37. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763 [published Online First: 2014/02/21]
38. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2017;69(6):807-16. doi: 10.1002/acr.23013 [published Online First: 2016/08/27]
39. Podmore B, Hutchings A, van der Meulen J, et al. Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis. *BMJ Open* 2018;8(7):e021784. doi: 10.1136/bmjopen-2018-021784 [published Online First: 2018/07/13]
40. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;47(6):805-13. doi: 10.1016/j.semarthrit.2017.10.016 [published Online First: 2017/11/22]
41. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *Bmj* 2015;350:h1225. doi: 10.1136/bmj.h1225 [published Online First: 2015/04/02]
42. Verkleij SP, Luijsterburg PA, Willemsen SP, et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. *Br J Gen Pract* 2015;65(637):e530-7. doi: 10.3399/bjgp15X686101 [published Online First: 2015/07/28]
43. WHO Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-medication. WHO/EDM/QSM/00.1. 2000. Available at: https://apps.who.int/medicinedocs. Accessed September 11, 2019.
44. Conaghan PG. NSAIDs or paracetamol for short-term treatment of mild to moderate knee pain in early osteoarthritis: are they equivalent? *Evid Based Med* 2016;21(1):14. doi: 10.1136/ebmed-2015-110289 [published Online First: 2015/10/21]
45. Deckers JG, Paget WJ, Schellevis FG, et al. European primary care surveillance networks: their structure and operation. *Fam Pract* 2006;23(2):151-8. doi: 10.1093/fampra/cmi118 [published Online First: 2006/02/09]
46. Trotter JP. Patient registries: a new gold standard for "real world" research. *Ochsner J* 2002;4(4):211-4. [published Online First: 2002/10/01]
47. Alpert JM, Krist AH, Aycock RA, et al. Designing User-Centric Patient Portals: Clinician and Patients' Uses and Gratifications. *Telemed J E Health* 2017;23(3):248-53. doi: 10.1089/tmj.2016.0096 [published Online First: 2016/06/23]

Footnotes

Contributors: PM and DS performed the analyses, and DS, PV, RH, MS, FL, BV wrote the manuscript. DS, MS and BV are responsible for the study concept, design, the recruitment of subjects and acquisition of data. All authors participated in the interpretation of the data. All authors approved the final version of the manuscript.

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Data sharing statement: The dataset supporting the conclusions of this article is held at the University of Leuven, Belgium, and can be shared upon contacting the corresponding author.

Figure legends

1. Figure 1. The standardized and non-standardized prevalence of patients with knee osteoarthritis by age cohorts in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.
2. Figure 2. An overview of the observed and modeled trends in prevalence for men and women in the Intego registry (1996-2015). Observed (bullets) and modeled (trend line) age-standardized average annual percentage change (AAPC) in prevalence with 95% confidence intervals for time trends for patients with knee osteoarthritis in Intego register, 1996–2015. The AAPC is significantly different from zero at alpha = 0.05**.**
3. Figure 3. The standardized and non-standardized incidence of patients with knee osteoarthritis in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.

Supplementary file list

1. Supplementary file 1. Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015).
2. Supplementary file 2. Participation of GP practices in Intego (1996-2015).
3. Supplementary file 3. ICPC codes and description of codes for the disease count.
4. Supplementary file 4. ACT coding for pharmacological agents used in the management of knee osteoarthritis.
5. Supplementary file 5. Demographic characteristics of patients with knee osteoarthritis in Intego (1996, 2005 and 2015).
6. The Record checklist.

Table 1. Demographic characteristics and trends in prevalence and incidence of patients with knee osteoarthritis in the Intego registry (1996-2015).

	Year 1996*	**Year 2015***	**Overall trend*****	**Trend 1**		**Trend 2**		**Trend 3**	
	%	**%**	AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Prevalence									
Total	1.99	3.56	**2.5 [2.2;2.9]**	1996-2015	**2.5 [2.2;2.9]**				
Men	1.32	2.59	**3.1 [2.7;3.5]**	1996-2015	**3.1 [2.7;3.5]**				
Women	2.64	4.55	**2.4 [2.0;2.7]**	1996-2015	**2.4 [2.0;2.7]**				
Prevalence by age group**									
25-34	0.68	1.82	**4.7 [3.7;5.6]**	1996-2007	**7.7 [6.4;9.1]**	2007-2015	0.6 [-0.9;2.1]		
35-44	0.70	2.21	**5.5 [4.3;6.7]**	1996-2011	**4.5 [3.6;5.4]**	2011-2015	**9.5 [4.3;15.0]**		
45-54	1.55	3.14	**4.0 [3.3;4.8]**	1996-2011	**3.4 [2.8;4.0]**	2011-2015	**6.5 [3.2;10.0]**		
55-64	2.96	5.60	**3.0 [2.6;3.4]**	1996-2015	**3.0 [2.6;3.4]**				
65-74	6.08	8.97	**1.7 [1.3;2.2]**	1996-2015	**1.7 [1.3;2.2]**				
75-84	7.80	13.9	**2.6 [2.0;3.2]**	1996-2007	**3.6 [2.7;4.5]**	2007-2015	**1.2 [0.2;2.1]**		
≥ 85	6.27	15.0	**3.0 [2.4;3.5]**	1996-2015	**3.0 [2.4;3.5]**				
Incidence									
Total	0.42	0.38	-0.5 [-1.4;0.5]	1996-2006	**-2.6 [-4.0;-1.1]**	2006-2015	**1.9 [0.4;3.5]**		
Men	0.27	0.26	-0.2 [-1.4;1.1]	1996-2006	**-2.5 [-4.4;-0.5]**	2006-2015	**2.5 [0.5;4.5]**		
Women	0.58	0.49	-0.5 [-2.4;1.4]	1996-1999	**-8.7 [-16.2;-0.6]**	1999-2013	-0.4 [-1.2;0.5]	2013-2015	11.8 [-3.3;29.3]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval

* These percentages are standardized for the total Flemish population.

** Standardization was possible for the total population, but not for specific age cohorts.

*** Joinpoint regression modelling was used to estimate (A) APC in prevalence and incidence trends. Three possible trends were calculated during the 20-year study period.

Statistically significant differences for (A) APC are indicated in bold.

Table 2. Trends in multimorbidity of the patients with knee osteoarthritis in the Intego registry (1996-2015).

Variables	1996-2000		2001-2005		2006-2010		2011-2015*		p-value **
Mean age (± SD)	55.3	(21.9)	57.6	(20.5)	57.8	(19.8)	56.9	(19.8)	0.384
Women, n (%)	972	(65%)	1234	(65%)	1419	(64%)	1412	(62%)	0.05224
Incidence, n* **	1503		1912		2202		2288		
Comorbidities, n (%)									
Hypertension	359	(24%)	485	(25%)	623	(28%)	593	(26%)	0.0756
Diabetes	93	(6%)	161	(8%)	252	(11%)	346	(15%)	<0.001
CV events	323	(21%)	480	(25%)	597	(27%)	614	(27%)	<0.001
GI complication (ulcer)	28	(2%)	60	(3%)	59	(3%)	61	(3%)	0.3585
Renal failure	23	(2%)	70	(4%)	71	(3%)	66	(3%)	0.1025
Depression	141	(9%)	230	(12%)	259	(12%)	287	(13%)	0.009
Obesity	74	(5%)	101	(5%)	145	(7%)	191	(8%)	<0.001
Osteoporosis	57	(4%)	81	(4%)	107	(5%)	103	(5%)	0.2303
Cancer	29	(2%)	60	(3%)	59	(3%)	61	(3%)	<0.001
Asthma	125	(8%)	205	(11%)	328	(15%)	392	(17%)	<0.001
Substance abuse	4	(0%)	22	(1%)	31	(1%)	48	(2%)	<0.001
Disease burden, n	1.6267		1.8383		2.1848		2.3387		<0.001

Legend:

*** Four time intervals of five years were defined to evaluate trends for incident patients with knee osteoarthritis.**

**** *P-value* for the comorbidities was calculated with the Cochran-Armitage trend test; p-value for age was calculated with the Jonckheere-Terpstra trend test.**

***** Multimorbidity was measured for all incident cases with knee osteoarthritis.**

Table 3. Trends in medication use of patients with knee osteoarthritis in the Intego registry (1996-2015).

Group/ Medication	Prev. in 1996	Prev. in 2015	Overall trend	Trend 1		Trend 2		Trend 3¥	
			AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Acetaminophen	5.3	19.2	**6.7 [5.6-7.7]**	1996-2010	**8.0 [6.8-9.2]**	2010-2015	**3.1 [0.3;5.9]**		
Males	5.2	17.4	**5.8 [4.9-6.6]**						
Females	5.4	20.2	**7.0 [5.8-8.3]**	1996-2010	**8.7 [7.3;10.1]**	2010-2015	2.7 [-0.6;6.0]		
Oral NSAID (exclusion cox-2)	28.4	29.4	0.0 [-1.1;1.1]	1996-2002	-1.0 [-3.5;1.6]	2002-2008	2.4 [-0.1;5.0]	2008-2015	-1.2 [-2.4;0.1]
Males	28.6	28.8	0.5 [-0.2;1.2]	1996-2009	**1.1 [0.4;1.9]**	2009-2015	0.5 [-0.2;1.2]		
Females	28.3	29.6	0.3 [-0.1;0.8]						
Cox-2 selective NSAID	3.0	2.3	-7.7 [-36.0; 33.0]	2000-2004	-2.7 [-29.3;33.9]	2004-2007	-48.4 [-93.5; 309.5]	2007-2015	11.8 [-3.4;29.5]
Males	2.2	1.8	**-13.3 [-19.3;-6.7]**						
Females	3.4	2.7	-7.3 [-34.0;30.1]	2000-2004	-3.3 [-29.1;32.0]	2004-2007	-47.2 [-92.2; 257.6]	2007-2015	12.0 [-2.9;29.2]
Topical NSAID	7.8	5.9	-1.0 [-2.4; 0.4]	1996-2003	**-4.7 [-8.1;-1.2]**	2003-2015	1.2 [-0.0;2.4]		
Males	9.3	5.8	-0.9 [-2.2;0.5]						
Females	7.1	5.9	-0.8 [-2.3;0.7]	1996-2003	**-4.3 [-8.0;-0.4]**	2003-2015	1.3 [-0.0;2.6]		
Weak opioids	2.8	6.1	**4.0 [0.9;7.3]**	1996-1998	**36.3 [0.4;85.2]**	1998-2009	-0.9 [-2.3;0.5]	2009-2015	**4.0 [1.6;6.4]**
Males	1.5	5.2	**2.9 [1.5;4.4]**						
Females	3.3	6.7	2.8 [-0.0;5.7]	1996-2000	**14.7 [1.6;29.4]**	2000-2008	-3.2 [-6.4;0.2]	2008-2015	**3.5 [0.6;6.4]**
Strong opioids	2.5	4.3	1.9 [-0.4;4.3]	1996-2003	**9.0 [2.5;16.0]**	2003-2015	**-2.0 [-3.7;-0.3]**		
Males	1.7	3.6	-0.2 [-2.0; 1.6]						
Females	2.9	4.7	**2.3 [0.3;4.3]**	1996-2003	**10.0 [4.4;15.9]**	2003-2015	**-2.0 [-3.4;-0.5]**		
Parenteral glucocorticoids	9.1	8.1	-0.7 [-1.8;0.5]	1996-2005	**-2.1 [-3.5;-0.7]**	2005-2012	**2.7 [0.8;4.7]**	2012-2015	-4.1 [-9.2;1.2]
Males	8.1	8.6	**0.8 [0.0;1.6]**						
Females	9.6	7.9	**-1.3 [-2.6; 0.0]**	1996-2003	**-3.8 [-6.0;-1.5]**	2003-2012	**2.0 [0.6;3.4]**	2012-2015	-5.1 [-10.7;0.8]
Glucosamine*	0.6	1.8	**8.6 [2.4;15.1]**	2001-2004	**64.1 [25.0;115.3]**	2004-2011	**-9.6 [-14.3;-4.4]**	2011-2015	9.8 [-0.6:21.2]
Males	0.1	1.8	17.3 [-18.8; 69.5]	2001-2003	212.4 [-83.1;5664.3]	2003-2015	-0.4 [-4.8;4.2]		
Females	0.9	1.8	**6.8 [0.4;13.7]**	2001-2004	**56.7 [18.3;107.5]**	2004-2011	**-10.0 [-15.3;-4.3]**	2011-2015	8.2 [-3.6;21.4]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval; Prev., prevalence

***glucosamine: registration starts from 2001; cox-2 selective NSAID starts from 2000**

Bold: indicates that the (A)APC is significantly different from zero at the alpha= 0.05 level

¥= three possible time trends were computed with the joinpoint regression analysis. The corresponding time cohorts and APC are mentioned in these three columns

Figure 1.

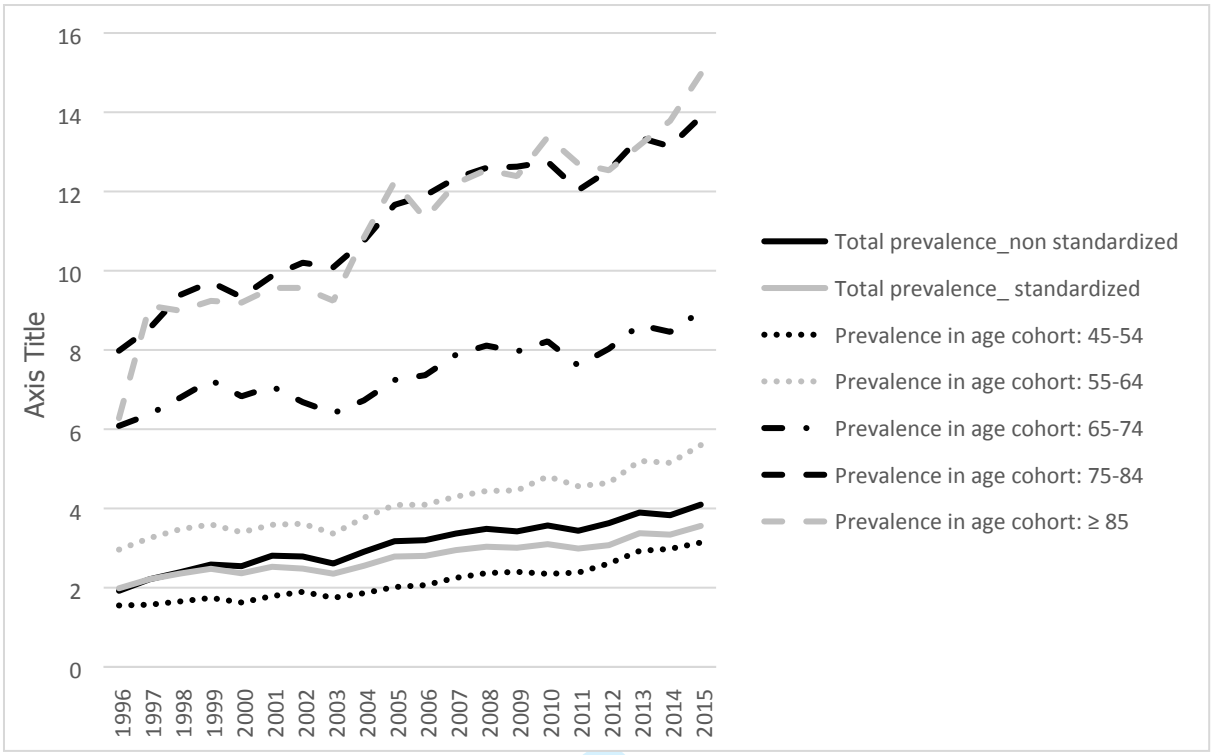


Figure 2.

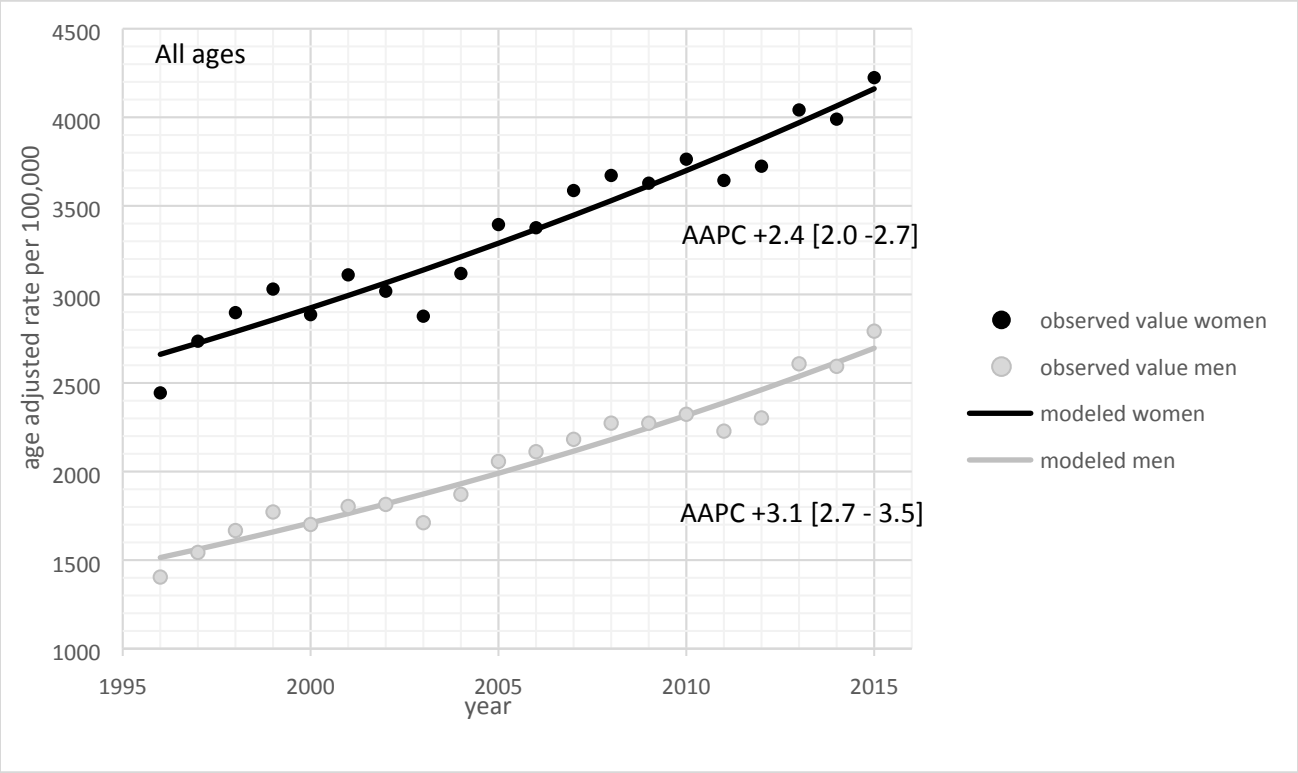
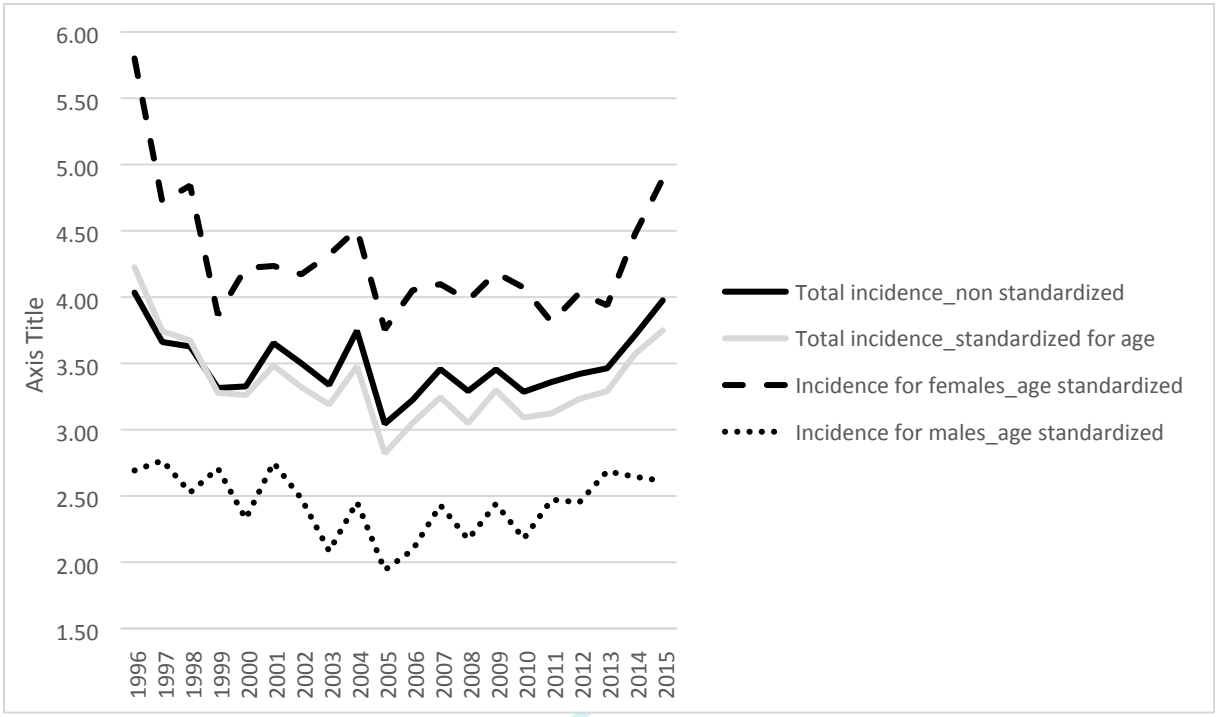


Figure 3.

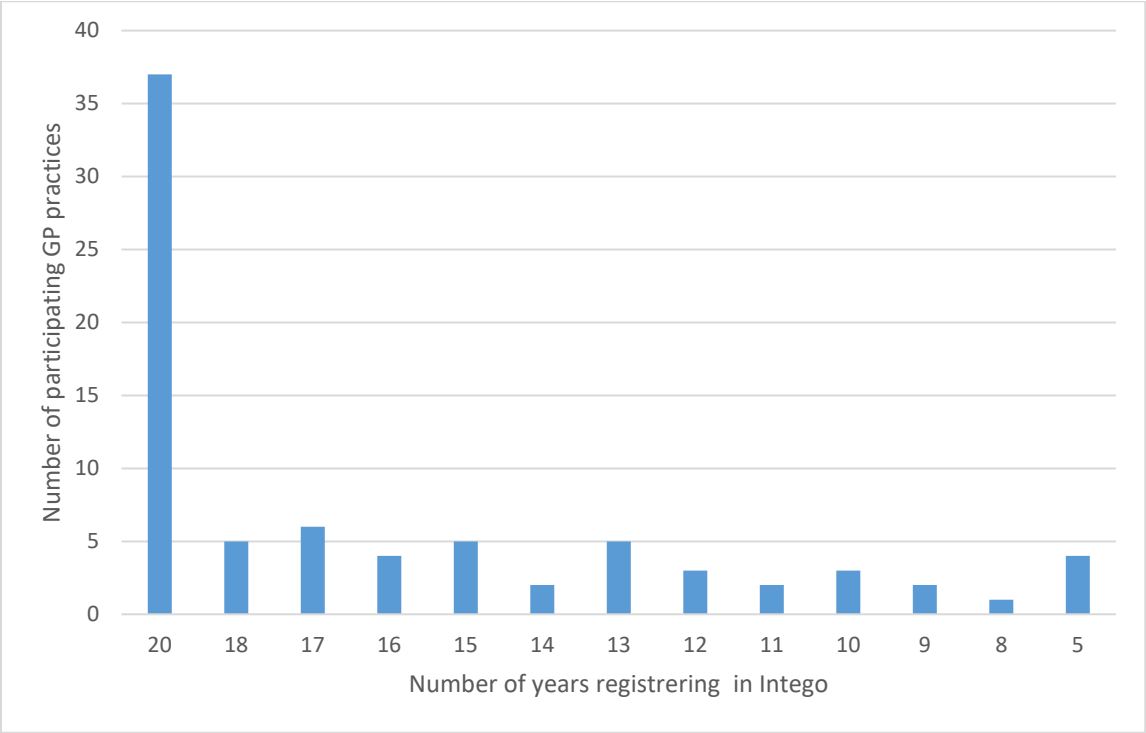


Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015)

Year	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Yearly contact group	83011	81763	85940	86535	95932	90973	106664	125202	120962	128251
Total prevalence knee osteoarthritis	1595	1809	2055	2236	2439	2554	2973	3268	3516	4069
By gender										
Male	39648	38927	40796	41252	45478	43325	50857	59759	57700	61446
Female	43363	42836	45144	45283	50454	47648	55807	65443	63262	66805
By age cohort										
≤ 14 year	13144	13180	13416	13044	13150	12585	15485	18458	17033	18223
15-24 year	10588	10532	11077	11162	12015	11652	13623	15966	15109	16071
25-34 year	14859	13322	13741	13243	14185	12899	14699	17477	16617	17538
35-44 year	13919	13462	14123	14240	16502	14404	16189	19282	18303	19040
45-54 year	9993	10315	11193	11599	13405	12812	14933	17469	17199	18450
55-64 year	8107	8148	8633	8675	9798	9729	11704	13731	13754	14826
65-74 year	7266	7357	7755	8027	9121	8943	10488	11961	11950	12247
75-84 year	3797	3955	4367	4694	5559	5785	7097	8218	8414	8900
≥ 85 year	1338	1492	1635	1851	2197	2164	2446	2640	2583	2956

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yearly contact group	133931	132322	134733	140259	140126	151971	127717	130398	131651	123261
Total prevalence Knee osteoarthritis	4284	4454	4695	4798	5003	5223	4635	5081	5041	5049
By gender										
Male	64012	63472	64423	67305	67075	72892	60829	62541	63404	58841
Female	69919	68850	70310	72954	73051	79079	66888	67857	68247	64420
By age cohort										
≤ 14 year	18928	18958	19145	20714	20531	22279	18728	19854	19711	19091
15-24 year	16841	16697	17065	17670	17483	18837	15337	15772	15962	14645
25-34 year	18551	18311	18916	20113	20003	21668	18264	18804	19578	17818
35-44 year	19640	18767	18672	19137	18627	19883	16597	16865	17434	15937
45-54 year	19379	19220	19595	20210	20345	22093	17972	18207	18220	16950
55-64 year	15512	15636	16054	16523	16827	18570	15657	15827	16037	15415
65-74 year	12372	12135	12108	12347	12363	13780	11505	11567	11494	11169
75-84 year	9305	9214	9439	9694	9835	10388	9070	8938	8601	8140
≥ 85 year	3403	3384	3739	3851	4112	4473	4587	4564	4614	4096

Participation of GP practices in Intego (1996-2015)



ICPC codes and description of codes for the disease count

Codes to measure the disease count

The combination of the following 92 ICPC-2 codes were used to measure the disease count. If codes are not mutually exclusive (e.g. T89 and T90), then they count for one.

ICPC code	Description
A79	Malignancy NOS
A90	Congenital anomaly OS/multiple
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B78	Hereditary haemolytic anaemia
B83	Purpura/coagulation defect
B90	HIV-infection/aids
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
F83	Retinopathy
F84	Macular degeneration
F94	Blindness
H83	Otosclerosis
H84	Presbyacusis
H86	Deafness
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K82	Pulmonary heart disease
K86	Hypertension uncomplicated
K87	Hypertension complicated
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L88	Reumatoãde arthritis
L89	Osteoarthrosis of hip
L90	Osteoarthrosis of knee
L91	Osteoarthrosis other
L95	Osteoporosis
L98	Acquired deformity of limb
N70	Poliomyelitis
N74	Malignant neoplasm nervous system
N85	Congenital anomaly neurological
N86	Multiple sclerosis
N87	Parkinsonism

N88	Epilepsy
N89	Migraine
N90	Cluster headache
N92	Trigeminal neuralgia
P15	Substance abuse: chronic alcohol
P28	Limited function/disability (p)
P70	Dementia
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P77	Suicide/suicide attempt
P79	Phobia/compulsive disorder
P80	Personality disorder
P85	Mental retardation
P98	Psychosis NOS/other
R79	Chronic bronchitis
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R95	Chronic obstructive pulmonary disease
R96	Asthma
S77	Malignant neoplasm of skin
S87	Dermatitis/atopic eczema
S91	Psoriasis
S97	Chronic ulcer skin
T71	Malignant neoplasm thyroid
T80	Congenital anom endocrine/metab.
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U04	Incontinence urine
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
W72	Malignant neoplasm relate to preg.
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malign neoplasm male genital other
Y85	Benign prostatic hypertrophy

Other ICPC codes used in this manuscript

ICPC code	description
P17	Substance abuse: tobacco
P19	Substance abuse: drug abuse
L89	Osteoarthritis of the hip
L90	Osteoarthritis of the knee
L91	Osteoarthritis of other locations (other than knee/hip)

ICPC codes used with Intego software to define comorbidity

Definition of cancer

Intego uses a set of 22 ICPC-2 codes to define cancer as a comorbidity: A79, B73, B72, B74, D74, D75, D76, D77, L71, N74, R84, R85, T71, U75, U76, U77, W72, X75, X76, X77, Y77, and Y78.

Definition of substance abuse

Intego uses a combination of three ICPC-2 codes to define substance abuse: P15, P 17, and P19.

ACT coding for pharmacological agents used in the management of knee osteoarthritis.

	ACT coding
Acetominophen	N02BE01
Oral NSAID (exclusion cox-2 selective)	M01AB M01AC-M01AE M01AG
COX-2 selective NSAID	M01AH
Topical NSAID	M02AA
Glucosamine supplements	M01AX05
Chondroitin supplements	M01AX25
Hyaluronic acid	M09AX01
Weak opioids	N02AX02 N02AJ01 N02AJ02 N02AJ03 N02AJ06 N02AJ07 N02AJ08 N02AJ09 N02AJ13 N02AJ14 N02AJ15
Strong opioids	N02AA N02AB N02AC N02AD N02AE N02AF
Glucocorticoids	H02AB

Demographic characteristics of patients with knee osteoarthritis in Intego registry (1996, 2005, and 2015).

	1996***		2005		2015	
	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized
Prevalence, gender						
Total	1.595/83011	1.92; 1.99	4069/128251	3.17;2.79	5049/123261	4.09; 3.56
Men	518/39648	1.31; 1.32	1348/61446	2.20;1.97	1817/58841	3.09; 2.59
Women	1077/43363	2.48; 2.64	2721/66805	4.07;3.67	3232/64420	5.02;4.55
Prevalence, age cohorts**						
25-34	101	0.68	272	1.55	324	1.82
35-44	98	0.70	225	1.18	353	2.22
45-54	155	1.55	372	2.01	532	3.13
55-64	240	2.96	606	4.08	863	5.60
65-74	442	6.08	887	7.24	1002	9.00
75-84	303	7.98	1038	11.66	1130	13.9
≥ 85	84	6.28	362	12.24	613	15.0
Incidence, gender						
Total	325/81416	0.40; 0.42	378/124182	0.30;0.28	470/118212	0.40; 0.38
Men	102/39130	0.26; 0.27	129/60098	0.21;0.19	167/57024	0.29; 0.26
Women	223/42286	0.53; 0.58	249/64084	0.39;0.38	303/61188	0.50;0.49

Legend:

N=yearly contact group: the number of patients that visited their general practitioner at least once during once year

***the first % refers to the age-specific data from the Intego register; the second % is the standardized Intego data for the total Flemish population.**

**** Standardization was possible for the total population, but not for specific age cohorts.**

***** Data are available for 20-year period. In this table 10-year interval periods are described.**

The RECORD statement

Checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Title (Title page and abstract) 1.2 Geographic region: abstract 1.3 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, p.2, paragraph 1-4
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, p.2, paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, p. 3, design

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods, pp. 3-4, design and data collection
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1 Methods, p. 3, supplementary file 3 for the ICPC codes and supplementary file 4 for the ACT codes 6.2 Intego registry external validation described in Truyers et al. Reference 6.3 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1 Methods, p. 3, design, supplementary file 1 till 4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Page 5: Methods, design pp. 3-4, the Intego

		Describe comparability of assessment methods if there is more than one group			Database is explained in detail
Bias	9	Describe any efforts to address potential sources of bias			Methods, design, p.3 and Discussion, pp. 11-12, paragraph 5
Study size	10	Explain how the study size was arrived at			NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods, data analysis p.5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			(a) methods, data analysis p.5 (b) NA (c) NA (d) NA (e) NA
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the	12.1 Data sharing statement, p.14

				investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2 Availability of data and materials, p.14
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	NA
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Results, pp. 6-9 Table 1 Figures 1-3 (b) NA (c) NA

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			(a) Results, pp. 6-9 Table 1-3 Figures 1-3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			NA
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion, last paragraph with conclusions p.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Discussion, paragraph 5, pp. 11-12

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, pp. 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, pp. 10-12
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Funding, p.14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials, p.14

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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The epidemiology of knee osteoarthritis in general practice: a registry-based study

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The epidemiology of knee osteoarthritis in general practice: a registry-based study

Abstract

Objectives The present study investigated (i) trends in the prevalence and incidence of knee osteoarthritis over a 20-year period; (ii) trends in multimorbidity; and (iii) trends in drug prescriptions.

Design Registry-based study.

Setting Primary health care, Flanders, Belgium.

Participants Data were collected from Intego, a general practice-based morbidity registration network. In the study period between 1996 and 2015 data from 440,140 unique patients were available.

Outcome measures Trends in prevalence and incidence rate of knee osteoarthritis were computed using joinpoint regression analysis. The mean disease count was calculated to assess trends in multimorbidity. In addition, the number of drug prescriptions was identified by the Anatomical Therapeutic Chemical Classification code and trends were equally recorded with joinpoint regression.

Results The prevalence of knee osteoarthritis increased from 1.99% in 1996 to 3.56% in 2015. An upward trend was observed with an average annual percentage change (AAPC) of 2.5 (95%CI 2.2-2.9). The incidence remained stable with 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5). The mean disease count significantly increased from 1.63 to 2.34 ($p<0.001$) for incident cases with knee osteoarthritis. Finally, we observed a significantly positive trend in the overall prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1).

Conclusions Increased prevalence, multimorbidity, and number of drug prescriptions confirm an increased burden of knee osteoarthritis. In future, these trends can be used to prioritize initiatives for improvement in care.

Key Words

Knee osteoarthritis; multimorbdity; general practice; trends; burden of illness

Article Summary

Strengths and limitations of this study

- The Intego open registry provides real-world data of 440,140 unique patients in a primary care setting, representative for the Flemish population.
- This registry, with data over a 20-year time period (1996-2015), lends itself for trend analyses.
- Estimates on the prevalence and incidence of knee osteoarthritis are scarce for primary care settings. This study defines knee osteoarthritis when it becomes a healthcare problem for the patient.
- Data completeness depends on the quality of registration of the participating general practitioners. To this end, only optimal registration practices are included in the Intego database.
- The lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes.

Introduction

Osteoarthritis (OA) is the most common joint disease and is expected to become the fourth leading cause of disability worldwide by 2020.[1] OA mainly affects the joints of the knees, hips, hands, facets and feet, but knee OA accounts for 83% of the total OA burden.[2] The prevalence of knee OA varies according to the definition: from subjective (population-based) assessments to clinical and radiographic definitions, often with low levels of concordance between them.[3] However, estimates on the prevalence of knee OA are scarce for primary care settings.[4]

At present, the purposes of conservative knee OA treatment are to alleviate pain, to improve the function of the joint and to slow down joint damage by pharmacological and non-pharmacological means.[5] All patients should be offered the following core conservative interventions: information to enhance their understanding about OA, advice to exercise, and to achieve weight loss for people who are obese or overweight.[6 7] Pharmacological management is dominated both by acetaminophen and by nonsteroidal anti-inflammatory drugs (NSAIDs).[5 8 9] The presence of multimorbidity may also affect choices in the pharmacological management, since multimorbidity and polypharmacy are closely related.[6 10 11] OA has one of the highest rates of multimorbidity for patients who are managed in general practice.[12 13]. Common multimorbidities in patients with knee OA are cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and obesity.[14] Nevertheless, multimorbidity-adapted management protocols are being developed and provide tailored guidance for pharmacological management and exercise therapy.[5 7] Numerous reports indicate that the number of people suffering from chronic diseases, multimorbidity and polypharmacy continues to increase, but those studies are mainly based on cross-sectional studies in different populations.[15] Time trends in the prevalence of multimorbidity and polypharmacy are scare.[16 17] The Flemish primary care-based Intego database offers the opportunity to extract “real world” data and evaluate time trends.

The aims of the present study were 1) to evaluate time trends in the prevalence and incidence of patients with knee OA managed in general practice; 2) to assess trends in multimorbidity and 3) to assess trends in drug prescriptions over a 20-year period.

Methods

Data source

This trend analysis study was performed using Intego, a general practice-based morbidity registration network in Flanders, Belgium.[18] The Intego database comprises data extracted from electronic health records (EHR) of general practitioners (GPs), all using the medical software programme Medidoc (Corilus NV, Aalter, Belgium).[19] Systematic collection of data started in 1994. In 2015, 111 GPs of 48 practices evenly spread throughout Flanders, collaborated in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The design, selection process, quality control procedures and comparability with other (inter)national registration networks were described in detail previously.[18] The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results, some background information (including gender and year of birth) and some biomedical parameters (i.e. blood pressure, height, weight, smoking status and mortality), using computer-generated keywords internally linked to codes. With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus and automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[20] Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.[21]

Study population

For the present study, data over a 20-year time interval from 1 January 1996 to 31 December 2015 were used. In this period, 440,140 unique patients were registered in the Intego database. The yearly contact group (=YCG) is defined as the number of different patients who consulted their GP in a given year.[22] During the study period, the YCG varied between 81,763 and 151,971 people (see supplementary file 1 for the exact number per year). Throughout the study period, 79 GP practices provided their data, with 72% contributing for 15 or more years (see supplementary file 2). This study was reported in accordance with the RECORD checklist specific to observational studies using routinely collected health data.[23]

Measures

Data on prevalence and incidence

Patients with knee OA were identified based on an ICPC-2 coded diagnosis in their EHR. The prevalence of a population is the proportion of the population with the disease at a specified time. Unlike incidence rates, which focus on new events, prevalence focuses on existing states. Because of the design of Intego (no episode registration and no recording of cure), prevalence rates could only be calculated on incurable chronic diseases, such as knee OA.[18] The incidence in Intego is calculated as the number of new cases of disease divided by the person-time magnitude. Calculating disease prevalence and incidence requires both a numerator (number of events or persons with a disease) and a matching denominator (the 'population at risk' being studied). Determining primary care practice denominators is challenging.[24] In this study, the YCG was used as denominator for all time trend analyses.[22]

Data on multimorbidity

Patients' medical history before they presented with knee OA was registered for all cases between 1996 and 2015. There are several instruments available to calculate multimorbidity, for example, the Carlson Index, the Cumulative Illness Rating Scale, the Index of Coexistent Diseases and the Kaplan Index.[25-28] For this study, the disease count was calculated for all incident cases with knee OA. For this disease count, a list of chronic diseases based on the paper by Knottnerus et al was used.[29] For the presence of chronic kidney disease (CKD), the glomerular filtration rate (GFR) was based on the closest creatinine measurement in the two years before or after presentation with knee OA diagnosis (Supplementary file 3: ICPC codes for diagnosis and multimorbidity).

Data on drug prescriptions

The prescription of medication for knee OA, including acetaminophen, oral and topical anti-inflammatory drugs, cox-2 selective anti-inflammatory drugs, weak and strong opioids, parenteral glucocorticoids, parenteral hyaluronic acid and glucosamine was extracted from Intego for all prevalent cases with knee OA (Supplementary file 4: used ACT codes). Prescription of medication was considered positive if it was prescribed at least once a year.

Statistical analysis

Descriptive statistics, with frequency distribution and percentages, were used to measure the prevalence (/100 patients) and incidence (/1000 patient years at risk) of patients with knee OA. Data were stratified by gender and ten-year age cohorts, starting from 25 with 85 years and older as the last cohort. The rates were age-standardized by taking the Flemish population of the year 1996 as reference population.[30] Additionally, possible time trends were analysed in the age-standardized cohorts with joinpoint regression analysis.[31] Joinpoint analysis identifies the best-fitting point, where a statistically significant change (called the "joinpoint") occurs, and determines the trends between joinpoints. Joinpoint regression allows us to identify the time point(s) of follow-up at which trends significantly change.[32] A

minimum number of three observations from a joinpoint to either end of the data, and a minimum number of four observations between two joinpoints were required.[33] The annual percentage change (APC) is proposed to summarize and compare the rates of changes between successive change points.[34] In the final model, the joinpoint analysis also provides an average annual percentage change (AAPC) as an average of APC estimates.[34] This means that trends over a specific period were described by the annual percent change (APC), while trends over the whole 1996–2015 period were summarised using the average annual percent change (AAPC). Analysis was performed with the Joinpoint Regression Program (version 3.5.3, released in May 2013 and available at http://surveillance.cancer.gov/joinpoint). This program starts with the minimum number of joinpoint (e.g. zero joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model. This enables the user to test that an apparent change in trend is statistically significant.

Trends in the multimorbidity profile for incident cases with knee OA were explored over four time intervals of five years (1996-2000, 2001-2005, 2006-2010 and 2011-2015) by the Cochran-Armitage test and the Jonckheere-Terpstra test. The Cochran-Armitage test for trend analysis is a modified Pearson's chi-square test to assess the association between binary and ordinal categories (e.g. between multimorbidities and time intervals). The Jonckheere-Terpstra trend test was used to analyse trends for continuous variables (e.g. between age and time intervals).[35]

Over the same 20-year time period, trends in drug prescriptions for prevalent cases with knee OA were analyzed using joinpoint regression analysis, as described above. Two-sided p-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using R Software Version 3.3.2 (Free Software Foundation Inc., Boston, MA, USA).

Patient involvement

No patients were involved in defining the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of the results.

Results

Demographic characteristics and trends in the prevalence and incidence of patients with knee osteoarthritis (1996-2015)

Between 1 January 1996 and 31 December 2015, the Intego database included data on 440,140 unique patients. Table 1 shows the demographic characteristics of the patients with knee OA by gender and age cohorts in Table 1.The age-standardized prevalence of knee OA increased by 79% from 1.99% in 1996 to 3.56% in 2015 (AAPC= 2.5, 95%CI 2.2-2.9, Figure 1 and supplementary file 5). Woman have a higher prevalence than men do, but over the 20 years of the study men have a higher relative increase in prevalence (AAPC= 3.1, 95%CI 2.7-3.5 for men versus AAPC= 2.4, 95%CI 2.0-2.7 for women).

Figure 2 presents the observed and modeled long-term time trends in prevalence by gender. The age-standardized incidence of patients with knee OA remained stable with 4.23‰ in 1996 and 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5), but showed a positive trend between 2006 and 2015 from 3.05‰ to 3.75‰, respectively (APC= 1.9, 95%CI 0.4-3.5) (Figure 3). Between 2006 and 2015, this positive trend was higher for men (APC= 2.5, 95%CI 0.5-4.5) than for women (APC= 1.9, 95%CI 0.4-3.5) (Figure 3).

Trends in multimorbidity in newly diagnosed patients with knee osteoarthritis (1996-2015)

In the 20-year study period, the mean age at diagnosis of knee OA remained stable (p=0.384) with 55.3 years in 1996 and 56.9 years in 2015, respectively, while a non-significant decline was found in the proportion of women in this period (65% to 62%, p=0.052). Additionally, the disease burden was defined by calculating the mean disease count of patients with knee OA.[29] This mean disease count showed a significant increase in the study period ranging from 1.6 to 2.3 (p<0.001), meaning that the multimorbidity of patients with knee OA increased. In this study, the following other diseases increased significantly: the proportions of patients with diabetes (6% to 15%, p<0.001), cardiovascular events (21% to 27%, p<0.001), depression (9% to 13%, p=0.009) and obesity (5% to 8%, p<0.001). Hypertension, gastro-intestinal ulcer and renal failure remained stable. Additionally, we noted that the proportion of knee OA patients with cancer (2% to 3%, p<0.001), asthma (8% to 17%, p<0.001) and substance abuse (0% to 2%, p<0.001) increased significantly during the study period, while the proportion with osteoporosis remained stable (Table 2).

Trends in prescriptions for patients with knee osteoarthritis (1996-2015)

The prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1) for patients with knee OA increased during the study period (Table 3). The prevalence of patients with knee OA who were prescribed acetaminophen was lower than those with oral NSAIDs (19.2% versus 29.4% in 2015; 5.3% versus 28.4% in 1996). The prescription of oral, topical and cox-2 selective NSAIDs remained stable for both genders during the study period. The use of strong opioids showed a strong increase between 1996 and 2003 (AAPC= 9.0, 95%CI 2.5-16), but then decreased slightly in the period from 2003 to 2015 (AAPC= -2.0, 95%CI 3.7 to -0.3).

Discussion

This study presents estimates of knee OA prevalence and incidence based on a large morbidity registration network for general practice in Belgium. During the 20-year study period, the age-standardized prevalence of knee OA significantly increased while the age-standardized incidence rate remained stable. During the study period, patients with knee OA experienced higher multimorbidity, as

shown by almost a doubling of the disease count. Oral NSAIDs were most frequently prescribed for the prevalent patients with knee OA, while prescription of acetaminophen, weak opioids and glucosamine showed an overall positive trend.

This study shows that the prevalence rate of knee OA significantly increased even after standardization of the study population. General practice morbidity registration networks in other European countries show similar rates for knee OA: in the Netherlands, an overall prevalence of 3.4% and incidence of 3.2‰ was registered in 2016.[36] In our study, we found similar rates with 3.56% and 3.75‰ respectively for the year 2015. In the UK, the estimated proportion of people who sought treatment for knee OA is high: 18% of the population aged 45 and over consulted their GP for knee OA.[37] In our study, we found a consultation prevalence of 21% for the same reference year (2010) and age cohorts. The latter study also found that OA is the most common musculoskeletal condition in older people and that just over half of all patients consulting their GP about OA have knee OA. In the near future, the number of people with knee OA is expected to rise considerably because of an aging population and obesity trends.[38] Nevertheless, the increasing prevalence of knee OA in general practice registration could also be attributed to other factors, for example: better access to general practice, more awareness of the public of preventive medicine, better diagnostics, better registration and higher demands and expectations of older people to remain physically active. Future qualitative research with different stakeholders could assess these possible explanations.

Osteoarthritis is one of the diseases with the highest rate of multimorbidity, with reported rates of 68% to 85%.[39 40] Coexisting disorders may worse pain and bring additional impairments, which necessitate adaptations to the conservative management of knee OA.[14 41] In our study, knee OA was also strongly associated with the following multimorbidities: asthma, cancer, depression and substance abuse. The substantial contribution of OA to multimorbidity and frailty should be recognized, further investigated, and needs extra attention in general practice management of long-term conditions.

Pharmacological management of knee OA in general practice is dominated both by acetaminophen and by NSAIDs, as they are both recommended in evidence-based guidelines.[5 7-9] In Intego we look at the GP's prescription and not the actual drug use by the patient. Although the review by Machado et al. suggested that acetaminophen has little clinical benefit in OA, guidelines recommend starting with acetaminophen, because the adverse side effect profile of NSAIDs.[42] In our study, NSAIDs were the most frequently prescribed pain drug for prevalent patients with knee OA. Verkleij et al. observed the effects of medication on 104 patients with knee OA in general practice. They demonstrated no significant difference regarding knee pain and knee function between patients taking diclofenac or acetaminophen.[43] Furthermore, the discrepancy between drug prescription by the professional and drug use by the patient can be accumulated by the over the counter availability of acetaminophen and some oral NSAID in Belgium. Over the counter availability, could be considered as part of self-care to reduce

the burden on health care systems and increase people's choice to take informed treatment decisions, but the medical outcome resulting from therapeutic options bypassing the physician prescription stays a major issue.[44] If acetaminophen should remain the ''first-line' pharmacological treatment for patients with a new episode, the effects of acetaminophen and the role in patients with multimorbidity should be further investigated.[45]

Strengths and limitations

The major strengths of this study are the long-term follow-up data of a practice-based morbidity registration network in general practice. Intego covers more than 2% of the Flemish population, representative in terms of age and gender.[18] Deckers et al. updated an inventory of primary care surveillance networks in Europa and formulated minimal standard criteria for these networks.[46] When fulfilling identical minimal criteria networks can provide comparable estimates of morbidity, ultimately leading to improved national and European surveillance. For continuous surveillance networks, they advise that a sufficient sample size is approximately 1% of the population, which will allow the study of common diseases.[46] Longitudinal data in registry-based studies are used to track the natural history of diseases over time and enable us to perform time-to-event analyses. In addition, general practices have to pass three quality criteria before being accepted as participants in Intego, what results in a reliable morbidity database.[18] Important attributes of most patient registries are their large sample size and data variability.[47] A few limitations must also be considered. Lack of data verification is a common problem in registry-based studies with longitudinal data of large sample size. In Intego, the lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes with a detailed thesaurus, individual patients are followed over time and their history is taken into account. The change for misclassification for knee OA was higher in younger age cohorts. If diagnoses are not mutually exclusive, then they count for one. Secondly, we are aware that accurate coding is always a risk for possible underdiagnosis. The difference between early-onset knee OA and chronic, established knee OA can not be established with the ICPC codes. Standardized coding for OA should be adopted in general practice to accurately describe the extent of the condition and to maximize the conservative management options to improve quality of life. Furthermore, there is no obligation for patients to be registered with a particular GP in Belgium. Therefore, it can be difficult to define 'the population at risk' for epidemiological studies in general practice. In Intego, the YCG was used as denominator for all trend analyses. Importantly, mortality data are lacking in Intego. Therefore, patients in the incidence analysis are considered at risk until the diagnosis or until December 31 of any specific year to compensate for possible overestimation in this registry-based study. Finally, obesity and smoking status could not be reliably assessed from the Intego database, because of insufficient registration in the patient files. To date, the information on socioeconomic status on patient level in the Intego register can not yet be extracted for data-analysis.. This information is available on practice level and based on the postal code. However, since GP practices in Flanders often take care of patients living

in neighboring municipalities and people living within a specific postal code can have a different socioeconomic status, we in general do not use this information in our analyses. Quality improvement initiatives should make GPs more aware of the necessity of properly recording up-to-date patient variables, such as BMI, in the EHR because of their growing importance in patient-tailored management strategies. Patient portals and remote access to their own medical health record are future initiatives, where the patient could play a more central role to help the GP in keeping these parameters more up-to-date by shared responsibility.[48]

Conclusion and recommendations

In conclusion, increased prevalence, multimorbidity, and number of drug prescriptions, together with the young age at incidence, confirm the high burden of knee OA. Our registry-based study represents knee OA diagnoses at a time it becomes a health issue for patients. Professionals face more difficulties in their conservative management options due to rising multimorbidity. In future, these health trends can be used to prioritize initiatives for improvement in care.

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References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/S0140-6736(12)61689-4
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2
3. Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185-99. doi: 10.1093/bmb/lds038
4. Bedson J, Jordan K, Croft P. The prevalence and history of knee osteoarthritis in general practice: a case-control study. *Fam Pract* 2005;22(1):103-8. doi: 10.1093/fampra/cmh700 [published Online First: 2005/01/11]
5. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22(3):363-88. doi: 10.1016/j.joca.2014.01.003 [published Online First: 2014/01/28]
6. National Institute for Health and Care Excellence (NICE): Osteoarthritis: care and management (quality standard 87): http://guidance.nice.org.uk/qs87. Accessed October 22, 2019.
7. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72(7):1125-35. doi: 10.1136/annrheumdis-2012-202745 [published Online First: 2013/04/19]
8. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64(4):465-74. [published Online First: 2012/05/09]
9. Kingsbury SR, Gross HJ, Isherwood G, et al. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014;53(5):937-47. doi: 10.1093/rheumatology/ket463 [published Online First: 2014/02/04]

10. Harding PA, Holland AE, Hinman RS, et al. Physical activity perceptions and beliefs following total hip and knee arthroplasty: a qualitative study. *Physiother Theory Pract* 2015;31(2):107-13. doi: 10.3109/09593985.2014.959581 [published Online First: 2014/12/17]
11. de Rooij M, Steultjens MPM, Avezaat E, et al. Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity. *Physical Therapy Reviews* 2013;18(2):101-11. doi: 10.1179/1743288X12Y.0000000056
12. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis* 2004;63(4):408-14. doi: 10.1136/ard.2003.007526 [published Online First: 2004/03/17]
13. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61 [published Online First: 2014/04/09]
14. Reeuwijk KG, de Rooij M, van Dijk GM, et al. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? *Clin Rheumatol* 2010;29(7):739-47. doi: 10.1007/s10067-010-1392-8 [published Online First: 2010/02/24]
15. Freid VM, Bernstein AB, Bush MA. Multiple chronic conditions among adults aged 45 and over: trends over the past 10 years. *NCHS Data Brief* 2012(100):1-8. [published Online First: 2012/10/30]
16. van den Akker M, Vaes B, Goderis G, et al. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. *PLoS One* 2019;14(2):e0212046. doi: 10.1371/journal.pone.0212046 [published Online First: 2019/02/13]
17. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14 Suppl 1:28-32. doi: 10.1080/13814780802436093 [published Online First: 2008/10/31]
18. Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48. doi: 10.1186/1472-6947-14-48 [published Online First: 2014/06/08]
19. Vanbeselaere V, Truyers C, Elli S, et al. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. *BMC Cardiovasc Disord* 2016;16:61. doi: 10.1186/s12872-016-0235-1 [published Online First: 2016/03/30]
20. Okkes IM, Becker HW, Bernstein RM, et al. The March 2002 update of the electronic version of ICPC-2. A step forward to the use of ICD-10 as a nomenclature and a terminology for ICPC-2. *Fam Pract* 2002;19(5):543-6. [published Online First: 2002/10/03]
21. WHO Collaborating Centre for Drug Statistics Methodology: ATC/DDD Index 2010. Available at http://www.whocc.no/atc_ddd_index. Accessed October 19, 2019.
22. Bartholomeeusen S, Kim CY, Mertens R, et al. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22(4):442-7. doi: 10.1093/fampra/cmi054 [published Online First: 2005/06/21]
23. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]
24. Greiver M, Williamson T, Bennett TL, et al. Developing a method to estimate practice denominators for a national Canadian electronic medical record database. *Fam Pract* 2013;30(3):347-54. doi: 10.1093/fampra/cms083 [published Online First: 2013/01/12]
25. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. [published Online First: 1987/01/01]
26. Shah AN, Vail TP, Taylor D, et al. Comorbid illness affects hospital costs related to hip arthroplasty: quantification of health status and implications for fair reimbursement and surgeon comparisons. *J Arthroplasty* 2004;19(6):700-5. [published Online First: 2004/09/03]

27. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968;16(5):622-6. doi: 10.1111/j.1532-5415.1968.tb02103.x [published Online First: 1968/05/01]
28. Piccirillo JF, Lacy PD, Basu A, et al. Development of a new head and neck cancer-specific comorbidity index. *Arch Otolaryngol Head Neck Surg* 2002;128(10):1172-9. doi: 10.1001/archotol.128.10.1172 [published Online First: 2002/10/09]
29. Knottnerus JA, Metsemakers J, Hoppener P, et al. Chronic illness in the community and the concept of 'social prevalence'. *Fam Pract* 1992;9(1):15-21. [published Online First: 1992/03/01]
30. Truyens C, Elli S, Goderis G, et al. [Dutch: 20 year General Practice in Flanders (1994-2013)]. Leuven: Acco, 2015. ISBN978-94-6292-129-0.
31. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. [published Online First: 2000/01/29]
32. Rea F, Pagan E, Compagnoni M, et al. Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies. *Epidemiology Biostatistics and Public Health* 2017;14(3):e12616:1-8.
33. Yu B, Barrett MJ, Kim H-J, et al. Estimating joinpoints in continuous time scale for multiple change-point models. *Computational Statistics & Data Analysis* 2007;51(5):2420-27. doi: https://doi.org/10.1016/j.csda.2006.07.044
34. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;28(29):3670-82. doi: 10.1002/sim.3733 [published Online First: 2009/10/27]
35. Alan A. Categorical data analysis. 2nd ed: Wiley 2002.
36. Nivel database for primary care morbidity registration in the Netherlands. Available at https://www.nivel.nl/nl/. Accessed October 19, 2019.
37. Osteoarthritis in general practice: data and perspectives. 2013. Available at www.arthritisresearchuk.org. Accessed October 19, 2019.
38. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763 [published Online First: 2014/02/21]
39. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2017;69(6):807-16. doi: 10.1002/acr.23013 [published Online First: 2016/08/27]
40. van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord* 2008;9:95. doi: 10.1186/1471-2474-9-95 [published Online First: 2008/06/28]
41. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;47(6):805-13. doi: 10.1016/j.semarthrit.2017.10.016 [published Online First: 2017/11/22]
42. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *Bmj* 2015;350:h1225. doi: 10.1136/bmj.h1225 [published Online First: 2015/04/02]
43. Verkleij SP, Luijsterburg PA, Willemsen SP, et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. *Br J Gen Pract* 2015;65(637):e530-7. doi: 10.3399/bjgp15X686101 [published Online First: 2015/07/28]
44. WHO Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-medication. WHO/EDM/QSM/00.1. 2000. Available at: https://apps.who.int/medicinedocs. Accessed September 11, 2019.
45. Conaghan PG. NSAIDs or paracetamol for short-term treatment of mild to moderate knee pain in early osteoarthritis: are they equivalent? *Evid Based Med* 2016;21(1):14. doi: 10.1136/ebmed-2015-110289 [published Online First: 2015/10/21]

46. Deckers JG, Paget WJ, Schellevis FG, et al. European primary care surveillance networks: their structure and operation. *Fam Pract* 2006;23(2):151-8. doi: 10.1093/fampra/cmi118 [published Online First: 2006/02/09]
47. Trotter JP. Patient registries: a new gold standard for "real world" research. *Ochsner J* 2002;4(4):211-4. [published Online First: 2002/10/01]
48. Alpert JM, Krist AH, Aycock RA, et al. Designing User-Centric Patient Portals: Clinician and Patients' Uses and Gratifications. *Telemed J E Health* 2017;23(3):248-53. doi: 10.1089/tmj.2016.0096 [published Online First: 2016/06/23]

Footnotes

Contributors: PM and DS performed the analyses, and DS, PV, RH, MS, FL, BV wrote the manuscript. DS, MS and BV are responsible for the study concept, design, the recruitment of subjects and acquisition of data. All authors participated in the interpretation of the data. All authors approved the final version of the manuscript.

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Ethics approval: The Intego project was presented to the Belgian Privacy Commission (no SCSZG/13/079) and approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723). This permission completely covered the current investigation. In the Intego protocol, participating GP practices have to inform their patients that the practice participates in a morbidity registration network. Patients can choose to opt out for the possibility of their anonymized data extraction.

Data sharing statement: The dataset supporting the conclusions of this article is held at the University of Leuven, Belgium, and can be shared upon contacting the corresponding author.

Figure legends

1. Figure 1. The standardized and non-standardized prevalence of patients with knee osteoarthritis by age cohorts in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.
2. Figure 2. An overview of the observed and modeled trends in prevalence for men and women in the Intego registry (1996-2015). Observed (bullets) and modeled (trend line) age-standardized average annual percentage change (AAPC) in prevalence with 95% confidence intervals for time trends for patients with knee osteoarthritis in Intego register, 1996–2015. The AAPC is significantly different from zero at alpha = 0.05**.**
3. Figure 3. The standardized and non-standardized incidence of patients with knee osteoarthritis in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.

Supplementary file list

1. Supplementary file 1. Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015).
2. Supplementary file 2. Participation of GP practices in Intego (1996-2015).
3. Supplementary file 3. ICPC codes and description of codes for the disease count.
4. Supplementary file 4. ACT coding for pharmacological agents used in the management of knee osteoarthritis.
5. Supplementary file 5. Demographic characteristics of patients with knee osteoarthritis in Intego (1996, 2005 and 2015).
6. The Record checklist.

Table 1. Demographic characteristics and trends in prevalence and incidence of patients with knee osteoarthritis in the Intego registry (1996-2015).

	Year 1996*	**Year 2015***	**Overall trend*****	**Trend 1**		**Trend 2**		**Trend 3**	
	%	**%**	AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Prevalence									
Total	1.99	3.56	**2.5 [2.2;2.9]**	1996-2015	**2.5 [2.2;2.9]**				
Men	1.32	2.59	**3.1 [2.7;3.5]**	1996-2015	**3.1 [2.7;3.5]**				
Women	2.64	4.55	**2.4 [2.0;2.7]**	1996-2015	**2.4 [2.0;2.7]**				
Prevalence by age group**									
25-34	0.68	1.82	**4.7 [3.7;5.6]**	1996-2007	**7.7 [6.4;9.1]**	2007-2015	0.6 [-0.9;2.1]		
35-44	0.70	2.21	**5.5 [4.3;6.7]**	1996-2011	**4.5 [3.6;5.4]**	2011-2015	**9.5 [4.3;15.0]**		
45-54	1.55	3.14	**4.0 [3.3;4.8]**	1996-2011	**3.4 [2.8;4.0]**	2011-2015	**6.5 [3.2;10.0]**		
55-64	2.96	5.60	**3.0 [2.6;3.4]**	1996-2015	**3.0 [2.6;3.4]**				
65-74	6.08	8.97	**1.7 [1.3;2.2]**	1996-2015	**1.7 [1.3;2.2]**				
75-84	7.80	13.9	**2.6 [2.0;3.2]**	1996-2007	**3.6 [2.7;4.5]**	2007-2015	**1.2 [0.2;2.1]**		
≥ 85	6.27	15.0	**3.0 [2.4;3.5]**	1996-2015	**3.0 [2.4;3.5]**				
Incidence									
Total	0.42	0.38	-0.5 [-1.4;0.5]	1996-2006	**-2.6 [-4.0;-1.1]**	2006-2015	**1.9 [0.4;3.5]**		
Men	0.27	0.26	-0.2 [-1.4;1.1]	1996-2006	**-2.5 [-4.4;-0.5]**	2006-2015	**2.5 [0.5;4.5]**		
Women	0.58	0.49	-0.5 [-2.4;1.4]	1996-1999	**-8.7 [-16.2;-0.6]**	1999-2013	-0.4 [-1.2;0.5]	2013-2015	11.8 [-3.3;29.3]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval

* These percentages are standardized for the total Flemish population.

** Standardization was possible for the total population, but not for specific age cohorts.

*** Joinpoint regression modelling was used to estimate (A) APC in prevalence and incidence trends. Three possible trends were calculated during the 20-year study period.

Statistically significant differences for (A) APC are indicated in bold.

Table 2. Trends in multimorbidity of patients with knee osteoarthritis in the Intego registry (1996-2015).

Variables	1996-2000		2001-2005		2006-2010		2011-2015*		p-value **
Mean age (± SD)	55.3	(21.9)	57.6	(20.5)	57.8	(19.8)	56.9	(19.8)	0.384
Women, n (%)	972	(65%)	1234	(65%)	1419	(64%)	1412	(62%)	0.05224
Incidence, n	1503		1912		2202		2288		
Multimorbidity, n (%)									
Hypertension	359	(24%)	485	(25%)	623	(28%)	593	(26%)	0.0756
Diabetes	93	(6%)	161	(8%)	252	(11%)	346	(15%)	<0.001
CV events	323	(21%)	480	(25%)	597	(27%)	614	(27%)	<0.001
GI complication (ulcer)	28	(2%)	60	(3%)	59	(3%)	61	(3%)	0.3585
Renal failure	23	(2%)	70	(4%)	71	(3%)	66	(3%)	0.1025
Depression	141	(9%)	230	(12%)	259	(12%)	287	(13%)	0.009
Obesity	74	(5%)	101	(5%)	145	(7%)	191	(8%)	<0.001
Osteoporosis	57	(4%)	81	(4%)	107	(5%)	103	(5%)	0.2303
Cancer	29	(2%)	60	(3%)	59	(3%)	61	(3%)	<0.001
Asthma	125	(8%)	205	(11%)	328	(15%)	392	(17%)	<0.001
Substance abuse	4	(0%)	22	(1%)	31	(1%)	48	(2%)	<0.001
Disease burden, n (± SD)* **	1.63	(1.81)	1.84	(2.00)	2.18	(2.20)	2.34	(2.35)	<0.001

Legend:

*** Four time intervals of five years were defined to evaluate trends for incident patients with knee osteoarthritis.**

**** *P-value* for multimorbidity was calculated with the Cochran-Armitage trend test; p-value for age was calculated with the Jonckheere-Terpstra trend test.**

***** The full list of diseases to calculate this mean disease burden is presented in supplementary file 3.**

Table 3. Trends in medication use of patients with knee osteoarthritis in the Intego registry (1996-2015).

Group/ Medication	Prev. in 1996	Prev. in 2015	Overall trend	Trend 1		Trend 2		Trend 3¥	
			AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Acetaminophen	5.3	19.2	**6.7 [5.6-7.7]**	1996-2010	**8.0 [6.8-9.2]**	2010-2015	**3.1 [0.3;5.9]**		
Males	5.2	17.4	**5.8 [4.9-6.6]**						
Females	5.4	20.2	**7.0 [5.8-8.3]**	1996-2010	**8.7 [7.3;10.1]**	2010-2015	2.7 [-0.6;6.0]		
Oral NSAID (exclusion cox-2)	28.4	29.4	0.0 [-1.1;1.1]	1996-2002	-1.0 [-3.5;1.6]	2002-2008	2.4 [-0.1;5.0]	2008-2015	-1.2 [-2.4;0.1]
Males	28.6	28.8	0.5 [-0.2;1.2]	1996-2009	**1.1 [0.4;1.9]**	2009-2015	0.5 [-0.2;1.2]		
Females	28.3	29.6	0.3 [-0.1;0.8]						
Cox-2 selective NSAID	3.0	2.3	-7.7 [-36.0; 33.0]	2000-2004	-2.7 [-29.3;33.9]	2004-2007	-48.4 [-93.5; 309.5]	2007-2015	11.8 [-3.4;29.5]
Males	2.2	1.8	**-13.3 [-19.3;-6.7]**						
Females	3.4	2.7	-7.3 [-34.0;30.1]	2000-2004	-3.3 [-29.1;32.0]	2004-2007	-47.2 [-92.2; 257.6]	2007-2015	12.0 [-2.9;29.2]
Topical NSAID	7.8	5.9	-1.0 [-2.4; 0.4]	1996-2003	**-4.7 [-8.1;-1.2]**	2003-2015	1.2 [-0.0;2.4]		
Males	9.3	5.8	-0.9 [-2.2;0.5]						
Females	7.1	5.9	-0.8 [-2.3;0.7]	1996-2003	**-4.3 [-8.0;-0.4]**	2003-2015	1.3 [-0.0;2.6]		
Weak opioids	2.8	6.1	**4.0 [0.9;7.3]**	1996-1998	**36.3 [0.4;85.2]**	1998-2009	-0.9 [-2.3;0.5]	2009-2015	**4.0 [1.6;6.4]**
Males	1.5	5.2	**2.9 [1.5;4.4]**						
Females	3.3	6.7	2.8 [-0.0;5.7]	1996-2000	**14.7 [1.6;29.4]**	2000-2008	-3.2 [-6.4;0.2]	2008-2015	**3.5 [0.6;6.4]**
Strong opioids	2.5	4.3	1.9 [-0.4;4.3]	1996-2003	**9.0 [2.5;16.0]**	2003-2015	**-2.0 [-3.7;-0.3]**		
Males	1.7	3.6	-0.2 [-2.0; 1.6]						
Females	2.9	4.7	**2.3 [0.3;4.3]**	1996-2003	**10.0 [4.4;15.9]**	2003-2015	**-2.0 [-3.4;-0.5]**		
Parenteral glucocorticoids	9.1	8.1	-0.7 [-1.8;0.5]	1996-2005	**-2.1 [-3.5;-0.7]**	2005-2012	**2.7 [0.8;4.7]**	2012-2015	-4.1 [-9.2;1.2]
Males	8.1	8.6	**0.8 [0.0;1.6]**						
Females	9.6	7.9	**-1.3 [-2.6; 0.0]**	1996-2003	**-3.8 [-6.0;-1.5]**	2003-2012	**2.0 [0.6;3.4]**	2012-2015	-5.1 [-10.7;0.8]
Glucosamine*	0.6	1.8	**8.6 [2.4;15.1]**	2001-2004	**64.1 [25.0;115.3]**	2004-2011	**-9.6 [-14.3;-4.4]**	2011-2015	9.8 [-0.6:21.2]
Males	0.1	1.8	17.3 [-18.8; 69.5]	2001-2003	212.4 [-83.1;5664.3]	2003-2015	-0.4 [-4.8;4.2]		
Females	0.9	1.8	**6.8 [0.4;13.7]**	2001-2004	**56.7 [18.3;107.5]**	2004-2011	**-10.0 [-15.3;-4.3]**	2011-2015	8.2 [-3.6;21.4]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval; Prev., prevalence

***glucosamine: registration starts from 2001; cox-2 selective NSAID starts from 2000**

Bold: indicates that the (A)APC is significantly different from zero at the alpha= 0.05 level

¥= three possible time trends were computed with the joinpoint regression analysis. The corresponding time cohorts and APC are mentioned in these three columns

Figure 1.

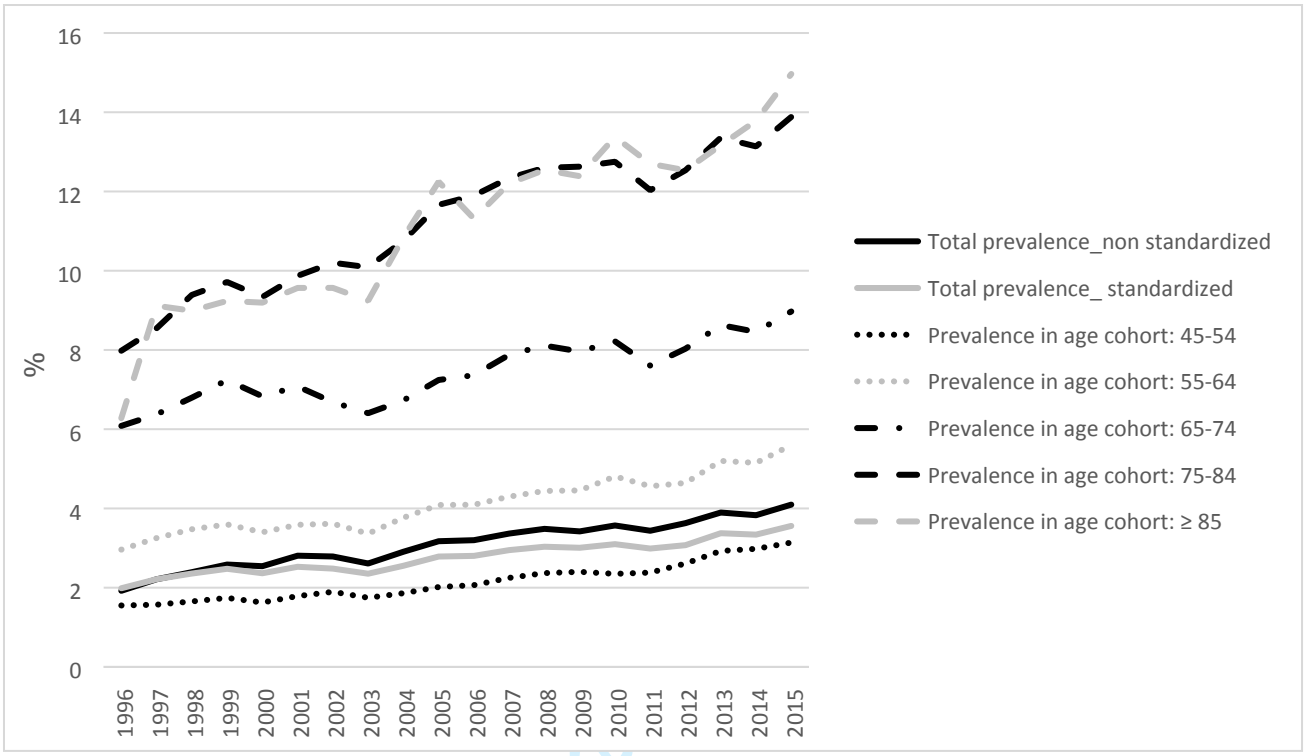


Figure 2.

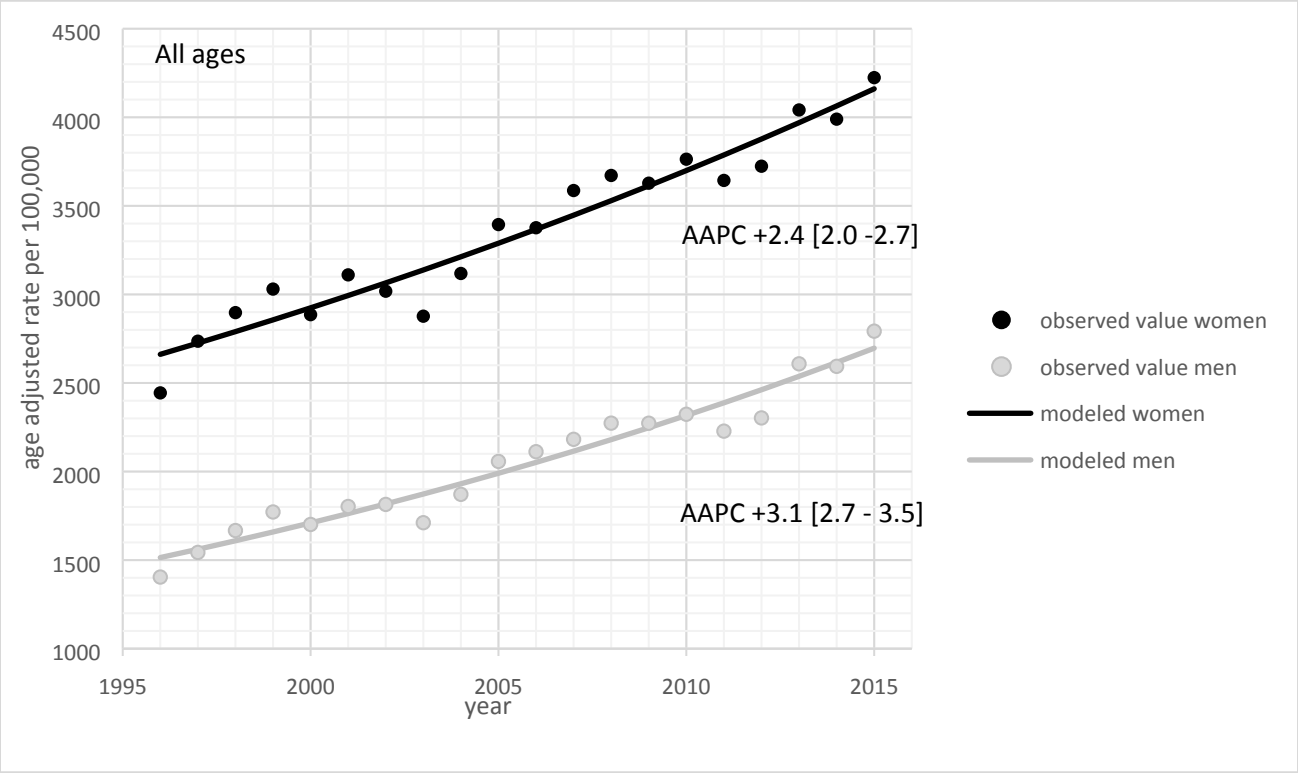
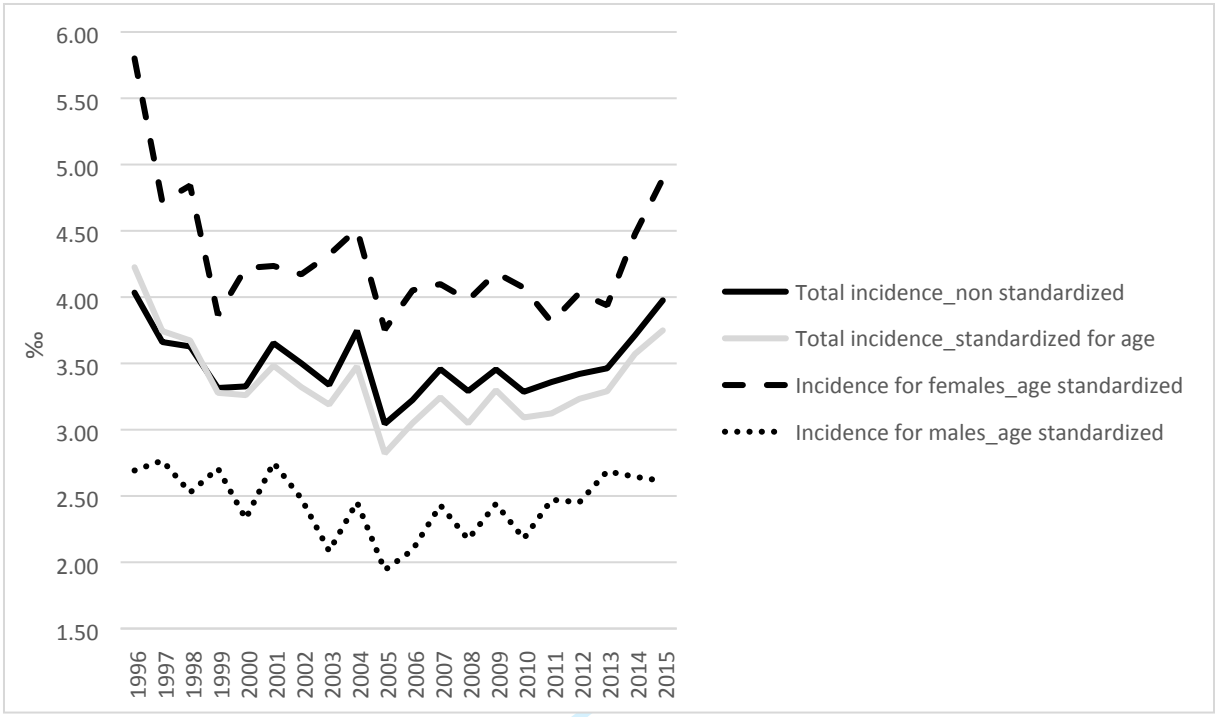


Figure 3.



Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015)

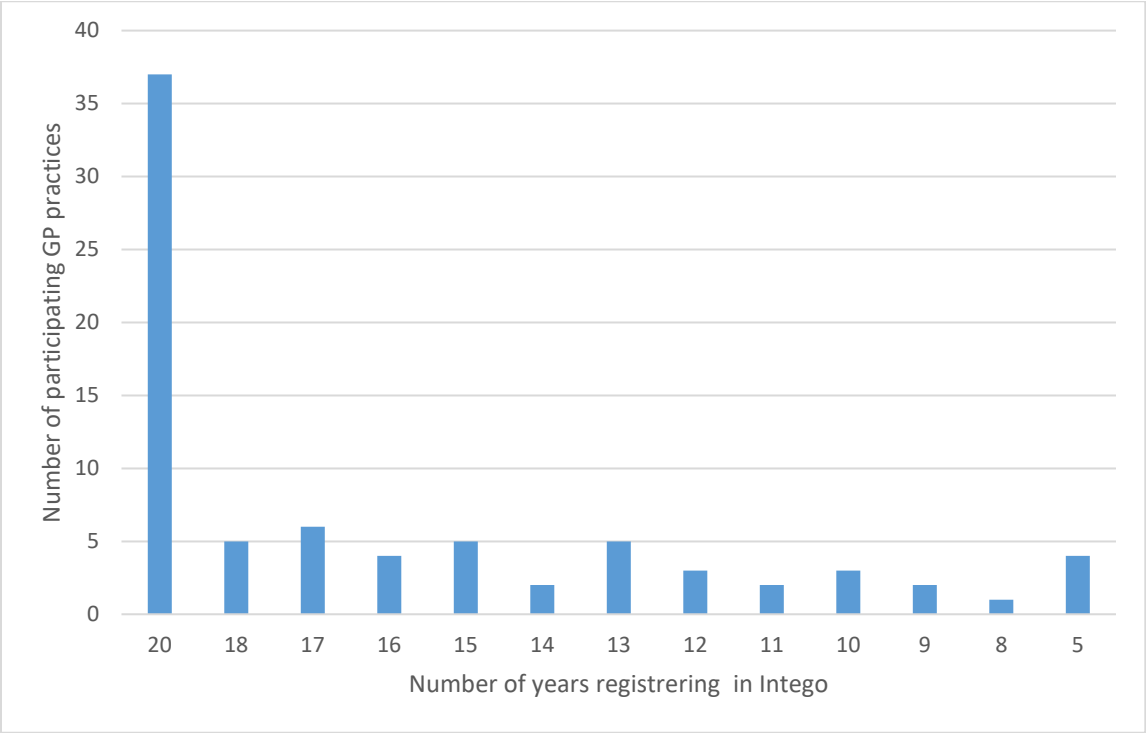
Year	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Yearly contact group	83011	81763	85940	86535	95932	90973	106664	125202	120962	128251
Total prevalence knee osteoarthritis*	1595 (1.92)	1809 (2.21)	2055 (2.39)	2236 (2.58)	2439 (2.54)	2554 (2.81)	2973 (2.79)	3268 (2.61)	3516 (2.91)	4069 (3.17)
By gender										
Male	39648	38927	40796	41252	45478	43325	50857	59759	57700	61446
Female	43363	42836	45144	45283	50454	47648	55807	65443	63262	66805
By age cohort										
≤ 24 year	23732	23712	24493	24206	25165	24237	29108	34424	32142	34294
25-34 year	14859	13322	13741	13243	14185	12899	14699	17477	16617	17538
35-44 year	13919	13462	14123	14240	16502	14404	16189	19282	18303	19040
45-54 year	9993	10315	11193	11599	13405	12812	14933	17469	17199	18450
55-64 year	8107	8148	8633	8675	9798	9729	11704	13731	13754	14826
65-74 year	7266	7357	7755	8027	9121	8943	10488	11961	11950	12247
75-84 year	3797	3955	4367	4694	5559	5785	7097	8218	8414	8900
≥ 85 year	1338	1492	1635	1851	2197	2164	2446	2640	2583	2956

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yearly contact group	133931	132322	134733	140259	140126	151971	127717	130398	131651	123261
Total prevalence Knee osteoarthritis*	4284 (3.20)	4454 (3.37)	4695 (3.48)	4798 (3.42)	5003 (3.57)	5223 (3.44)	4635 (3.63)	5081 (3.90)	5041 (3.83)	5049 (4.09)
By gender										
Male	64012	63472	64423	67305	67075	72892	60829	62541	63404	58841
Female	69919	68850	70310	72954	73051	79079	66888	67857	68247	64420
By age cohort										
≤ 24 year	35769	35655	36210	38384	38014	41116	34065	35626	35673	33736
25-34 year	18551	18311	18916	20113	20003	21668	18264	18804	19578	17818
35-44 year	19640	18767	18672	19137	18627	19883	16597	16865	17434	15937
45-54 year	19379	19220	19595	20210	20345	22093	17972	18207	18220	16950
55-64 year	15512	15636	16054	16523	16827	18570	15657	15827	16037	15415
65-74 year	12372	12135	12108	12347	12363	13780	11505	11567	11494	11169
75-84 year	9305	9214	9439	9694	9835	10388	9070	8938	8601	8140
≥ 85 year	3403	3384	3739	3851	4112	4473	4587	4564	4614	4096

Legend:

***(%) = proportion of patients with knee osteoarthritis. This proportion describes the data from the Intego registry and is not standardized for the total Flemish population.**

Participation of GP practices in Intego (1996-2015)



ICPC codes and description of codes for the disease count

Codes to measure the disease count

The combination of the following 92 ICPC-2 codes were used to measure the disease count. If codes are not mutually exclusive (e.g. T89 and T90), then they count for one.

ICPC code	Description
A79	Malignancy NOS
A90	Congenital anomaly OS/multiple
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B78	Hereditary haemolytic anaemia
B83	Purpura/coagulation defect
B90	HIV-infection/aids
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
F83	Retinopathy
F84	Macular degeneration
F94	Blindness
H83	Otosclerosis
H84	Presbyacusis
H86	Deafness
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K82	Pulmonary heart disease
K86	Hypertension uncomplicated
K87	Hypertension complicated
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L88	Reumatoãde arthritis
L89	Osteoarthrosis of hip
L90	Osteoarthrosis of knee
L91	Osteoarthrosis other
L95	Osteoporosis
L98	Acquired deformity of limb
N70	Poliomyelitis
N74	Malignant neoplasm nervous system
N85	Congenital anomaly neurological
N86	Multiple sclerosis
N87	Parkinsonism

N88	Epilepsy
N89	Migraine
N90	Cluster headache
N92	Trigeminal neuralgia
P15	Substance abuse: chronic alcohol
P28	Limited function/disability (p)
P70	Dementia
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P77	Suicide/suicide attempt
P79	Phobia/compulsive disorder
P80	Personality disorder
P85	Mental retardation
P98	Psychosis NOS/other
R79	Chronic bronchitis
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R95	Chronic obstructive pulmonary disease
R96	Asthma
S77	Malignant neoplasm of skin
S87	Dermatitis/atopic eczema
S91	Psoriasis
S97	Chronic ulcer skin
T71	Malignant neoplasm thyroid
T80	Congenital anom endocrine/metab.
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U04	Incontinence urine
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
W72	Malignant neoplasm relate to preg.
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malign neoplasm male genital other
Y85	Benign prostatic hypertrophy

Other ICPC codes used in this manuscript

ICPC code	description
P17	Substance abuse: tobacco
P19	Substance abuse: drug abuse
L89	Osteoarthritis of the hip
L90	Osteoarthritis of the knee
L91	Osteoarthritis of other locations (other than knee/hip)

ICPC codes used with Intego software to define multimorbidity

Definition of cancer

Intego uses a set of 22 ICPC-2 codes to define cancer as a multimorbidity: A79, B73, B72, B74, D74, D75, D76, D77, L71, N74, R84, R85, T71, U75, U76, U77, W72, X75, X76, X77, Y77, and Y78.

Definition of substance abuse

Intego uses a combination of three ICPC-2 codes to define substance abuse: P15, P 17, and P19.

ACT coding for pharmacological agents used in the management of knee osteoarthritis.

	ACT coding
Acetominophen	N02BE01
Oral NSAID (exclusion cox-2 selective)	M01AB M01AC-M01AE M01AG
COX-2 selective NSAID	M01AH
Topical NSAID	M02AA
Glucosamine supplements	M01AX05
Chondroitin supplements	M01AX25
Hyaluronic acid	M09AX01
Weak opioids	N02AX02 N02AJ01 N02AJ02 N02AJ03 N02AJ06 N02AJ07 N02AJ08 N02AJ09 N02AJ13 N02AJ14 N02AJ15
Strong opioids	N02AA N02AB N02AC N02AD N02AE N02AF
Glucocorticoids	H02AB

Demographic characteristics of patients with knee osteoarthritis in Intego registry (1996, 2005, and 2015).

	1996***		2005		2015	
	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized
Prevalence, gender						
Total	1.595/83011	1.92; 1.99	4069/128251	3.17;2.79	5049/123261	4.09; 3.56
Men	518/39648	1.31; 1.32	1348/61446	2.20;1.97	1817/58841	3.09; 2.59
Women	1077/43363	2.48; 2.64	2721/66805	4.07;3.67	3232/64420	5.02;4.55
Prevalence, age cohorts**						
≤ 24	172	1.59	307	1.89	232	1.56
25-34	101	0.68	272	1.55	324	1.82
35-44	98	0.70	225	1.18	353	2.22
45-54	155	1.55	372	2.01	532	3.13
55-64	240	2.96	606	4.08	863	5.60
65-74	442	6.08	887	7.24	1002	9.00
75-84	303	7.98	1038	11.66	1130	13.9
≥ 85	84	6.28	362	12.24	613	15.0
Incidence, gender						
Total	325/81416	0.40; 0.42	378/124182	0.30;0.28	470/118212	0.40; 0.38
Men	102/39130	0.26; 0.27	129/60098	0.21;0.19	167/57024	0.29; 0.26
Women	223/42286	0.53; 0.58	249/64084	0.39;0.38	303/61188	0.50;0.49

Legend:

N=yearly contact group: the number of patients that visited their general practitioner at least once during once year

***the first % refers to the age-specific data from the Intego register; the second % is the standardized Intego data for the total Flemish population.**

**** Standardization was possible for the total population, but not for specific age cohorts.**

***** Data are available for 20-year period. In this table 10-year interval periods are described.**

The RECORD statement

Checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Title (Title page and abstract) 1.2 Geographic region: abstract 1.3 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, p.2, paragraph 1-4
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, p.2, paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, p. 3, design

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods, pp. 3-4, design and data collection
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1 Methods, p. 3, supplementary file 3 for the ICPC codes and supplementary file 4 for the ACT codes 6.2 Intego registry external validation described in Truyers et al. Reference 6.3 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1 Methods, p. 3, design, supplementary file 1 till 4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Page 5: Methods, design pp. 3-4, the Intego

		Describe comparability of assessment methods if there is more than one group			Database is explained in detail
Bias	9	Describe any efforts to address potential sources of bias			Methods, design, p.3 and Discussion, pp. 11-12, paragraph 5
Study size	10	Explain how the study size was arrived at			NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods, data analysis p.5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			(a) methods, data analysis p.5 (b) NA (c) NA (d) NA (e) NA
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the	12.1 Data sharing statement, p.14

				investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2 Availability of data and materials, p.14
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	NA
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Results, pp. 6-9 Table 1 Figures 1-3 (b) NA (c) NA

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			(a) Results, pp. 6-9 Table 1-3 Figures 1-3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			NA
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion, last paragraph with conclusions p.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Discussion, paragraph 5, pp. 11-12

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, pp. 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, pp. 10-12
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Funding, p.14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials, p.14

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

The epidemiology of knee osteoarthritis in general practice: a registry-based study

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Primary Subject Heading:	Epidemiology
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The epidemiology of knee osteoarthritis in general practice: a registry-based study

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The epidemiology of knee osteoarthritis in general practice: a registry-based study

Abstract

Objectives The present study investigated (i) trends in the prevalence and incidence of knee osteoarthritis over a 20-year period (1996-2015); (ii) trends in multimorbidity; and (iii) trends in drug prescriptions.

Design Registry-based study.

Setting Primary health care, Flanders, Belgium.

Participants Data were collected from Intego, a general practice-based morbidity registration network. In the study period between 1996 and 2015 data from 440,140 unique patients were available.

Outcome measures Trends in prevalence and incidence rate of knee osteoarthritis were computed using joinpoint regression analysis. The mean disease count was calculated to assess trends in multimorbidity. In addition, the number of drug prescriptions was identified by the Anatomical Therapeutic Chemical Classification code and trends were equally recorded with joinpoint regression.

Results The total age-standardized prevalence of knee osteoarthritis increased from 2.0% in 1996 to 3.6% in 2015. An upward trend was observed with an average annual percentage change (AAPC) of 2.5 (95%CI 2.2-2.9). In 2015, the prevalence rates in the 10-year age groups from the 45-54 years age group onwards were 3.1%, 5.6%, 9.0% and 13.9%, to reach 15.0% in people aged 85 years and older. The incidence remained stable with 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5). The mean disease count significantly increased from 1.63 to 2.34 ($p<0.001$) for incident cases with knee osteoarthritis. Finally, we observed a significantly positive trend in the overall prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1). Oral NSAIDs were most prescribed, with a prevalence rate of 29.8% in 2015, but remained stable during the study period (AAPC=0.0, 95%CI -1.1-1.1).

Conclusions Increased prevalence, multimorbidity, and number of drug prescriptions confirm an increased burden of knee osteoarthritis. In future, these trends can be used to prioritize initiatives for improvement in care.

Key Words

Knee osteoarthritis; multimorbdity; general practice; trends; burden of illness

Article Summary

Strengths and limitations of this study

- The Intego open registry, with primary care data over a 20-year time period (1996-2015), is representative for the Flemish population and lends itself for trend analyses.
- Estimates on the prevalence and incidence of knee osteoarthritis are scarce for primary care settings. This study defines knee osteoarthritis when it becomes a healthcare problem for the patient.
- Data completeness depends on the quality of registration of the participating general practitioners. To this end, only optimal registration practices are included in the Intego database.
- The lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes.

Introduction

Osteoarthritis (OA) is the most common joint disease and is expected to become the fourth leading cause of disability worldwide by 2020.[1] OA mainly affects the joints of the knees, hips, hands, facets and feet, but knee OA accounts for 83% of the total OA burden.[2] The prevalence of knee OA varies according to the definition: from subjective (population-based) assessments to clinical and radiographic definitions, often with low levels of concordance between them.[3] However, estimates on the prevalence of knee OA are scarce for primary care settings.[4]

At present, the purposes of conservative knee OA treatment are to alleviate pain, to improve the function of the joint and to slow down joint damage by pharmacological and non-pharmacological means.[5] All patients should be offered the following core conservative interventions: information to enhance their understanding about OA, advice to exercise, and to achieve weight loss for people who are obese or overweight.[6 7] Pharmacological management is dominated both by acetaminophen and by nonsteroidal anti-inflammatory drugs (NSAIDs).[5 8 9] The presence of multimorbidity may also affect choices in the pharmacological management, since multimorbidity and polypharmacy are closely related.[6 10 11] OA has one of the highest rates of multimorbidity for patients who are managed in general practice.[12 13] Common multimorbidities in patients with knee OA are cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and obesity.[14] Nevertheless, multimorbidity-adapted management protocols are being developed and provide tailored guidance for pharmacological management and exercise therapy.[5 7] Numerous reports indicate that the number of people suffering from chronic diseases, multimorbidity and polypharmacy continues to increase, but those studies are mainly based on cross-sectional studies in different populations.[15] Time trends in the prevalence of multimorbidity and

polypharmacy are scare.[16 17] The Flemish primary care-based Intego database offers the opportunity to extract "real world" data and evaluate time trends.

The aims of the present study were 1) to evaluate time trends in the prevalence and incidence of patients with knee OA managed in general practice; 2) to assess trends in multimorbidity and 3) to assess trends in drug prescriptions over a 20-year period.

Methods

Data source

This trend analysis study was performed using Intego, a general practice-based morbidity registration network in Flanders, Belgium.[18] The Intego database comprises data extracted from electronic health records (EHR) of general practitioners (GPs), all using the medical software programme Medidoc (Corilus NV, Aalter, Belgium).[19] Systematic collection of data started in 1994. In 2015, 111 GPs of 48 practices evenly spread throughout Flanders, collaborated in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The design, selection process, quality control procedures and comparability with other (inter)national registration networks were described in detail previously.[18] The Intego GPs prospectively and routinely registered all new diagnoses using computer-generated keywords internally linked to codes together with new drug prescriptions, as well as laboratory test results, some background information (including gender and year of birth) and some biomedical parameters (i.e. blood pressure, height, weight, smoking status and mortality). With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a detailed thesaurus and automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[20] Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.[21]

Study population

For the present study, data over a 20-year time interval from 1 January 1996 to 31 December 2015 were used. Since Intego is an open registry, the amount of unique patients changes every year. The yearly contact group (YCG), defined as the number of unique patients who consult their GP in a given year, was used to describe the population at risk (denominator) in this study.[22] Throughout the study period, 79 GP practices provided their data, with 72% contributing for 15 or more years (see supplementary file

1). This study was reported in accordance with the RECORD checklist specific to observational studies using routinely collected health data.[23]

Measures

Data on prevalence and incidence

Patients with knee OA were identified based on an ICPC-2 coded diagnosis in their EHR. The prevalence of a population is the proportion of the population with the disease at a specified time. Unlike incidence rates, which focus on new events, prevalence focuses on existing states. Because of the design of Intego (no episode registration and no recording of cure), prevalence rates could only be calculated on incurable chronic diseases, such as knee OA.[18] The incidence in Intego is calculated as the number of new cases of disease divided by the person-time magnitude. Calculating disease prevalence and incidence requires both a numerator (number of events or persons with a disease) and a matching denominator (the 'population at risk' being studied). Determining primary care practice denominators is challenging.[24] In this study, the YCG was used as denominator for all time trend analyses.[22]

Data on multimorbidity

The Intego registry captures the historical diagnoses of an included patient, and not just the diagnoses made in the years the data were send to the repository. This means that all information on comorbid diseases is integrated at the time of patient's inclusion. There are several instruments available to calculate multimorbidity, for example, the Carlson Index, the Cumulative Illness Rating Scale, the Index of Coexistent Diseases and the Kaplan Index.[25-28] For this study, the disease count was calculated for all incident cases with knee OA (i.e. at the time when knee OA was registered as a diagnosis). For this disease count, a list of chronic diseases based on the paper by Knottnerus et al was used.[29] For the presence of chronic kidney disease (CKD), the glomerular filtration rate (GFR) was based on the closest creatinine measurement in the two years before or after presentation with knee OA diagnosis (Supplementary file 2: ICPC codes for diagnosis and multimorbidity).

Data on drug prescriptions

The prescription of medication for knee OA, including acetaminophen, oral and topical anti-inflammatory drugs, cox-2 selective anti-inflammatory drugs, weak and strong opioids, parenteral glucocorticoids, parenteral hyaluronic acid and glucosamine was extracted from Intego for all prevalent cases with knee OA (Supplementary file 3: used ACT codes). Prescription of medication was considered positive if it was prescribed at least once a year.

Statistical analysis

Descriptive statistics, with frequency distribution and percentages, were used to measure the prevalence (/100 patients) and incidence (/1000 patient years at risk) of patients with knee OA. Data were stratified by gender and ten-year age cohorts, starting from 25 with 85 years and older as the last cohort. The rates

were age-standardized by taking the Flemish population of the year 1996 as reference population.[30] Additionally, possible time trends were analysed in the age-standardized cohorts with joinpoint regression analysis.[31] Joinpoint analysis identifies the best-fitting point, where a statistically significant change (called the "joinpoint") occurs, and determines the trends between joinpoints. Joinpoint regression allows us to identify the time point(s) of follow-up at which trends significantly change.[32] A minimum number of three observations from a joinpoint to either end of the data, and a minimum number of four observations between two joinpoints were required.[33] The annual percentage change (APC) is proposed to summarize and compare the rates of changes between successive change points.[34] In the final model, the joinpoint analysis also provides an average annual percentage change (AAPC) as an average of APC estimates.[34] This means that trends over a specific period were described by the annual percent change (APC), while trends over the whole 1996–2015 period were summarised using the average annual percent change (AAPC). Analysis was performed with the Joinpoint Regression Program (version 3.5.3, released in May 2013 and available at http://surveillance.cancer.gov/joinpoint). This program starts with the minimum number of joinpoint (e.g. zero joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model. This enables the user to test that an apparent change in trend is statistically significant.

Trends in the multimorbidity profile for incident cases with knee OA were explored over four time intervals of five years (1996-2000, 2001-2005, 2006-2010 and 2011-2015) by the Cochran-Armitage test and the Jonckheere-Terpstra test. The Cochran-Armitage test for trend analysis is a modified Pearson's chi-square test to assess the association between binary and ordinal categories (e.g. between multimorbidities and time intervals). The Jonckheere-Terpstra trend test was used to analyse trends for continuous variables (e.g. between age and time intervals).[35]

Over the same 20-year time period, trends in drug prescriptions for prevalent cases with knee OA were analyzed using joinpoint regression analysis, as described above. Two-sided p-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using R Software Version 3.3.2 (Free Software Foundation Inc., Boston, MA, USA).

Patient involvement

No patients were involved in defining the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of the results.

Results

Demographic characteristics and trends in the prevalence and incidence of patients with knee osteoarthritis (1996-2015)

Between 1 January 1996 and 31 December 2015, the Intego database included data on 440,140 unique patients. During the study period, the YCG varied between 81,763 and 151,971 people (see supplementary file 4 for the exact number per year). Table 1 shows the demographic characteristics of the patients with knee OA by gender and age cohorts.The age-standardized prevalence of knee OA increased by 79% from 1.99% in 1996 to 3.56% in 2015 (AAPC= 2.5, 95%CI 2.2-2.9, Figure 1 and supplementary file 5). Woman have a higher prevalence than men do, but over the 20 years of the study men have a higher relative increase in prevalence (AAPC= 3.1, 95%CI 2.7-3.5 for men versus AAPC= 2.4, 95%CI 2.0-2.7 for women). Figure 2 presents the observed and modeled long-term time trends in prevalence by gender. The age-standardized incidence of patients with knee OA remained stable with 4.23‰ in 1996 and 3.75‰ in 2015 (AAPC=-0.5, 95%CI -1.4-0.5), but showed a positive trend between 2006 and 2015 from 3.05‰ to 3.75‰, respectively (APC= 1.9, 95%CI 0.4-3.5) (Figure 3). Between 2006 and 2015, this positive trend was higher for men (APC= 2.5, 95%CI 0.5-4.5) than for women (APC= 1.9, 95%CI 0.4-3.5) (Figure 3).

Trends in multimorbidity in newly diagnosed patients with knee osteoarthritis (1996-2015)

In the 20-year study period, the mean age at diagnosis of knee OA remained stable (p=0.384) with 55.3 years in 1996 and 56.9 years in 2015, respectively, while a non-significant decline was found in the proportion of women in this period (65% to 62%, p=0.052). Additionally, the disease burden was defined by calculating the mean disease count of patients with knee OA.[29] This mean disease count showed a significant increase in the study period ranging from 1.6 to 2.3 (p<0.001), meaning that the multimorbidity of patients with knee OA increased. In this study, the following other diseases increased significantly: the proportions of patients with diabetes (6% to 15%, p<0.001), cardiovascular events (21% to 27%, p<0.001), depression (9% to 13%, p=0.009) and obesity (5% to 8%, p<0.001). Hypertension, gastro-intestinal ulcer and renal failure remained stable. Additionally, we noted that the proportion of knee OA patients with cancer (2% to 3%, p<0.001), asthma (8% to 17%, p<0.001) and substance abuse (0% to 2%, p<0.001) increased significantly during the study period, while the proportion with osteoporosis remained stable (Table 2).

Trends in prescriptions for patients with knee osteoarthritis (1996-2015)

The prescription of acetaminophen (AAPC= 6.7, 95%CI 5.6-7.7), weak opioids (AAPC= 4.0, 95%CI 0.9-7.3) and glucosamine (AAPC= 8.6, 95%CI 2.4-15.1) for patients with knee OA increased during the study period (Table 3). The prevalence of patients with knee OA who were prescribed acetaminophen

was lower than those with oral NSAIDs (19.2% versus 29.4% in 2015; 5.3% versus 28.4% in 1996). The prescription of oral, topical and cox-2 selective NSAIDs remained stable for both genders during the study period. The use of strong opioids showed a strong increase between 1996 and 2003 (AAPC= 9.0, 95%CI 2.5-16), but then decreased slightly in the period from 2003 to 2015 (AAPC= -2.0, 95%CI 3.7 to -0.3).

Discussion

This study presents estimates of knee OA prevalence and incidence based on a large morbidity registration network for general practice in Belgium. During the 20-year study period, the age-standardized prevalence of knee OA significantly increased while the age-standardized incidence rate remained stable. During the study period, patients with knee OA experienced higher multimorbidity, as shown by almost a doubling of the disease count. Oral NSAIDs were most frequently prescribed for the prevalent patients with knee OA, while prescription of acetaminophen, weak opioids and glucosamine showed an overall positive trend.

This study shows that the prevalence rate of knee OA significantly increased even after standardization of the study population. General practice morbidity registration networks in other European countries show similar rates for knee OA: in the Netherlands, an overall prevalence of 3.4% and incidence of 3.2‰ was registered in 2016.[36] In our study, we found similar rates with 3.56% and 3.75‰ respectively for the year 2015. In the UK, the estimated proportion of people who sought treatment for knee OA is high: 18% of the population aged 45 and over consulted their GP for knee OA.[37] The latter study also found that OA is the most common musculoskeletal condition in older people and that just over half of all patients consulting their GP about OA have knee OA. In our study, we found a consultation prevalence of 21% for the same reference year (2010) and age cohorts. In the near future, the number of people with knee OA is expected to rise considerably because of an aging population and obesity trends.[38] Nevertheless, the increasing prevalence of knee OA in general practice registration could also be attributed to other factors, for example: better access to general practice, more awareness of the public of preventive medicine, better diagnostics, better registration and higher demands and expectations of older people to remain physically active. Future qualitative research with different stakeholders could assess these possible explanations.

Osteoarthritis is one of the diseases with the highest rate of multimorbidity, with reported rates of 68% to 85%.[39 40] Coexisting disorders may worse pain and bring additional impairments, which necessitate adaptations to the conservative management of knee OA.[14 41] In our study, knee OA was also strongly associated with the following multimorbidities: asthma, cancer, depression and substance abuse. The substantial contribution of OA to multimorbidity and frailty should be recognized, further investigated, and needs extra attention in general practice management of long-term conditions.

Pharmacological management of knee OA in general practice is dominated both by acetaminophen and by NSAIDs, as they are both recommended in evidence-based guidelines.[5 7-9] In Intego we look at the GP's prescription and not the actual drug use by the patient. Although the review by Machado et al. suggested that acetaminophen has little clinical benefit in OA, guidelines recommend starting with acetaminophen, because the adverse side effect profile of NSAIDs.[42] In our study, NSAIDs were the most frequently prescribed pain drug for prevalent patients with knee OA. Verkleij et al. observed the effects of medication on 104 patients with knee OA in general practice. They demonstrated no significant difference regarding knee pain and knee function between patients taking diclofenac or acetaminophen.[43] Furthermore, the discrepancy between drug prescription by the professional and drug use by the patient can be accumulated by the over the counter availability of acetaminophen and some oral NSAID in Belgium. Over the counter availability, could be considered as part of self-care to reduce the burden on health care systems and increase people's choice to take informed treatment decisions, but the medical outcome resulting from therapeutic options bypassing the physician prescription stays a major issue.[44] If acetaminophen should remain the ''first-line' pharmacological treatment for patients with a new episode, the effects of acetaminophen and the role in patients with multimorbidity should be further investigated.[45]

Strengths and limitations

The major strengths of this study are the long-term follow-up data of a practice-based morbidity registration network in general practice. Intego covers more than 2% of the Flemish population, representative in terms of age and gender.[18] Deckers et al. updated an inventory of primary care surveillance networks in Europa and formulated minimal standard criteria for these networks.[46] When fulfilling identical minimal criteria networks can provide comparable estimates of morbidity, ultimately leading to improved national and European surveillance. For continuous surveillance networks, they advise that a sufficient sample size is approximately 1% of the population, which will allow the study of common diseases.[46] Longitudinal data in registry-based studies are used to track the natural history of diseases over time and enable us to perform time-to-event analyses. In addition, general practices have to pass three quality criteria before being accepted as participants in Intego, what results in a reliable morbidity database.[18] Important attributes of most patient registries are their large sample size and data variability.[47] A few limitations must also be considered. Lack of data verification is a common problem in registry-based studies with longitudinal data of large sample size. In Intego, the lack of data verification and misclassification is minimalised because new diagnoses are automatically linked to ICPC-2 and ICD-10 codes with a detailed thesaurus, individual patients are followed over time and their history is taken into account. The change for misclassification for knee OA was higher in younger age cohorts. If diagnoses are not mutually exclusive, then they count for one. Secondly, we are aware that accurate coding is always a risk for possible underdiagnosis. The difference between early-onset knee OA and chronic, established knee OA can not be established with the ICPC codes. Standardized coding

for OA should be adopted in general practice to accurately describe the extent of the condition and to maximize the conservative management options to improve quality of life. Thirdly, there is no obligation for patients to be registered with a particular GP in Belgium. Therefore, it can be difficult to define 'the population at risk' for epidemiological studies in general practice. In Intego, the YCG was used as denominator for all trend analyses. Importantly, mortality data are lacking in Intego. Therefore, patients in the incidence analysis are considered at risk until the diagnosis or until December 31 of any specific year to compensate for possible overestimation in this registry-based study. Furthermore, to calculate the total prevalence and incidence rates, we used the total YCG as the denominator. Since age is an important risk factor to develop knee OA, younger unaffected individuals are probably overrepresented in the total population. This could result in an underestimation of the total prevalence and incidence rates. Therefore, we also provide these rates for all age cohorts in tables and supplementary files. Finally, obesity and smoking status could not be reliably assessed from the Intego database, because of insufficient registration in the patient files. To date, the information on socioeconomic status on patient level in the Intego register can not yet be extracted for data-analysis.This information is available on practice level and based on the postal code. However, since GP practices in Flanders often take care of patients living in neighboring municipalities and people living within a specific postal code can have a different socioeconomic status, we in general do not use this information in our analyses. Quality improvement initiatives should make GPs more aware of the necessity of properly recording up-to-date patient variables, such as BMI, in the EHR because of their growing importance in patient-tailored management strategies. Patient portals and remote access to their own medical health record are future initiatives, where the patient could play a more central role to help the GP in keeping these parameters more up-to-date by shared responsibility.[48]

Conclusion and recommendations

In conclusion, increased prevalence, multimorbidity, and number of drug prescriptions, together with the young age at incidence, confirm the high burden of knee OA. Our registry-based study represents knee OA diagnoses at a time it becomes a health issue for patients. Professionals face more difficulties in their conservative management options due to rising multimorbidity. In future, these health trends can be used to prioritize initiatives for improvement in care.

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References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/S0140-6736(12)61689-4

2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2
3. Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185-99. doi: 10.1093/bmb/lds038
4. Bedson J, Jordan K, Croft P. The prevalence and history of knee osteoarthritis in general practice: a case-control study. *Fam Pract* 2005;22(1):103-8. doi: 10.1093/fampra/cmh700 [published Online First: 2005/01/11]
5. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22(3):363-88. doi: 10.1016/j.joca.2014.01.003 [published Online First: 2014/01/28]
6. National Institute for Health and Care Excellence (NICE): Osteoarthritis: care and management (quality standard 87): http://guidance.nice.org.uk/qs87. Accessed October 22, 2019.
7. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72(7):1125-35. doi: 10.1136/annrheumdis-2012-202745 [published Online First: 2013/04/19]
8. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64(4):465-74. [published Online First: 2012/05/09]
9. Kingsbury SR, Gross HJ, Isherwood G, et al. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014;53(5):937-47. doi: 10.1093/rheumatology/ket463 [published Online First: 2014/02/04]
10. Harding PA, Holland AE, Hinman RS, et al. Physical activity perceptions and beliefs following total hip and knee arthroplasty: a qualitative study. *Physiother Theory Pract* 2015;31(2):107-13. doi: 10.3109/09593985.2014.959581 [published Online First: 2014/12/17]
11. de Rooij M, Steultjens MPM, Avezaat E, et al. Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity. *Physical Therapy Reviews* 2013;18(2):101-11. doi: 10.1179/1743288X12Y.0000000056
12. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis* 2004;63(4):408-14. doi: 10.1136/ard.2003.007526 [published Online First: 2004/03/17]
13. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61 [published Online First: 2014/04/09]
14. Reeuwijk KG, de Rooij M, van Dijk GM, et al. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? *Clin Rheumatol* 2010;29(7):739-47. doi: 10.1007/s10067-010-1392-8 [published Online First: 2010/02/24]
15. Freid VM, Bernstein AB, Bush MA. Multiple chronic conditions among adults aged 45 and over: trends over the past 10 years. *NCHS Data Brief* 2012(100):1-8. [published Online First: 2012/10/30]
16. van den Akker M, Vaes B, Goderis G, et al. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. *PLoS One* 2019;14(2):e0212046. doi: 10.1371/journal.pone.0212046 [published Online First: 2019/02/13]
17. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14 Suppl 1:28-32. doi: 10.1080/13814780802436093 [published Online First: 2008/10/31]
18. Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48. doi: 10.1186/1472-6947-14-48 [published Online First: 2014/06/08]

19. Vanbeselaere V, Truyers C, Elli S, et al. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. *BMC Cardiovasc Disord* 2016;16:61. doi: 10.1186/s12872-016-0235-1 [published Online First: 2016/03/30]
20. Okkes IM, Becker HW, Bernstein RM, et al. The March 2002 update of the electronic version of ICPC-2. A step forward to the use of ICD-10 as a nomenclature and a terminology for ICPC-2. *Fam Pract* 2002;19(5):543-6. [published Online First: 2002/10/03]
21. WHO Collaborating Centre for Drug Statistics Methodology: ATC/DDD Index 2010. Available at http://www.whocc.no/atc_ddd_index. Accessed October 19, 2019.
22. Bartholomeeusen S, Kim CY, Mertens R, et al. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22(4):442-7. doi: 10.1093/fampra/cmi054 [published Online First: 2005/06/21]
23. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]
24. Greiver M, Williamson T, Bennett TL, et al. Developing a method to estimate practice denominators for a national Canadian electronic medical record database. *Fam Pract* 2013;30(3):347-54. doi: 10.1093/fampra/cms083 [published Online First: 2013/01/12]
25. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. [published Online First: 1987/01/01]
26. Shah AN, Vail TP, Taylor D, et al. Comorbid illness affects hospital costs related to hip arthroplasty: quantification of health status and implications for fair reimbursement and surgeon comparisons. *J Arthroplasty* 2004;19(6):700-5. [published Online First: 2004/09/03]
27. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968;16(5):622-6. doi: 10.1111/j.1532-5415.1968.tb02103.x [published Online First: 1968/05/01]
28. Piccirillo JF, Lacy PD, Basu A, et al. Development of a new head and neck cancer-specific comorbidity index. *Arch Otolaryngol Head Neck Surg* 2002;128(10):1172-9. doi: 10.1001/archotol.128.10.1172 [published Online First: 2002/10/09]
29. Knottnerus JA, Metsemakers J, Hoppener P, et al. Chronic illness in the community and the concept of 'social prevalence'. *Fam Pract* 1992;9(1):15-21. [published Online First: 1992/03/01]
30. Truyens C, Elli S, Goderis G, et al. [Dutch: 20 year General Practice in Flanders (1994-2013)]. Leuven: Acco, 2015. ISBN978-94-6292-129-0.
31. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335-51. [published Online First: 2000/01/29]
32. Rea F, Pagan E, Compagnoni M, et al. Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies. *Epidemiology Biostatistics and Public Health* 2017;14(3):e12616:1-8.
33. Yu B, Barrett MJ, Kim H-J, et al. Estimating joinpoints in continuous time scale for multiple change-point models. *Computational Statistics & Data Analysis* 2007;51(5):2420-27. doi: https://doi.org/10.1016/j.csda.2006.07.044
34. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;28(29):3670-82. doi: 10.1002/sim.3733 [published Online First: 2009/10/27]
35. Alan A. Categorical data analysis. 2nd ed: Wiley 2002.
36. Nivel database for primary care morbidity registration in the Netherlands. Available at https://www.nivel.nl/nl/. Accessed October 19, 2019.
37. Osteoarthritis in general practice: data and perspectives. 2013. Available at www.arthritisresearchuk.org. Accessed October 19, 2019.
38. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763 [published Online First: 2014/02/21]

39. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2017;69(6):807-16. doi: 10.1002/acr.23013 [published Online First: 2016/08/27]
40. van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord* 2008;9:95. doi: 10.1186/1471-2474-9-95 [published Online First: 2008/06/28]
41. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;47(6):805-13. doi: 10.1016/j.semarthrit.2017.10.016 [published Online First: 2017/11/22]
42. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *Bmj* 2015;350:h1225. doi: 10.1136/bmj.h1225 [published Online First: 2015/04/02]
43. Verkleij SP, Luijsterburg PA, Willemsen SP, et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. *Br J Gen Pract* 2015;65(637):e530-7. doi: 10.3399/bjgp15X686101 [published Online First: 2015/07/28]
44. WHO Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-medication. WHO/EDM/QSM/00.1. 2000. Available at: https://apps.who.int/medicinedocs. Accessed September 11, 2019.
45. Conaghan PG. NSAIDs or paracetamol for short-term treatment of mild to moderate knee pain in early osteoarthritis: are they equivalent? *Evid Based Med* 2016;21(1):14. doi: 10.1136/ebmed-2015-110289 [published Online First: 2015/10/21]
46. Deckers JG, Paget WJ, Schellevis FG, et al. European primary care surveillance networks: their structure and operation. *Fam Pract* 2006;23(2):151-8. doi: 10.1093/fampra/cmi118 [published Online First: 2006/02/09]
47. Trotter JP. Patient registries: a new gold standard for "real world" research. *Ochsner J* 2002;4(4):211-4. [published Online First: 2002/10/01]
48. Alpert JM, Krist AH, Aycock RA, et al. Designing User-Centric Patient Portals: Clinician and Patients' Uses and Gratifications. *Telemed J E Health* 2017;23(3):248-53. doi: 10.1089/tmj.2016.0096 [published Online First: 2016/06/23]

Footnotes

Contributors: PM and DS performed the analyses, and DS, PV, RH, MS, FL, BV wrote the manuscript. DS, MS and BV are responsible for the study concept, design, the recruitment of subjects and acquisition of data. All authors participated in the interpretation of the data. All authors approved the final version of the manuscript.

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Ethics approval: The Intego project was presented to the Belgian Privacy Commission (no SCSZG/13/079) and approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723). This permission completely covered the current investigation. In the Intego protocol, participating GP practices have to inform their patients that the practice participates in a morbidity registration network. Patients can choose to opt out for the possibility of their anonymized data extraction.

Data sharing statement: The dataset supporting the conclusions of this article is held at the University of Leuven, Belgium, and can be shared upon contacting the corresponding author.

Figure legends

1. Figure 1. The standardized and non-standardized prevalence of patients with knee osteoarthritis by age cohorts in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.
2. Figure 2. An overview of the observed and modeled trends in prevalence for men and women in the Intego registry (1996-2015). Observed (bullets) and modeled (trend line) age-standardized average annual percentage change (AAPC) in prevalence with 95% confidence intervals for time trends for patients with knee osteoarthritis in Intego register, 1996–2015. The AAPC is significantly different from zero at alpha = 0.05**.**
3. Figure 3. The standardised and non-standardized incidence of patients with knee osteoarthritis in the Intego registry (1996-2015). Standardization was performed by taking the Flemish population of the year 1996 as reference population.

Supplementary file list

1. Supplementary file 1. Participation of GP practices in Intego (1996-2015).
2. Supplementary file 2. ICPC codes and description of codes for the disease count.
3. Supplementary file 3. ACT coding for pharmacological agents used in the management of knee osteoarthritis.
4. Supplementary file 4. Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015).
5. Supplementary file 5. Demographic characteristics of patients with knee osteoarthritis in Intego (1996, 2005 and 2015).

Table 1. Demographic characteristics and trends in prevalence and incidence of patients with knee osteoarthritis in the Intego registry (1996-2015).

	Year 1996*	**Year 2015***	**Overall trend*****	**Trend 1**		**Trend 2**		**Trend 3**	
	%	**%**	AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Prevalence									
Total	1.99	3.56	**2.5 [2.2;2.9]**	1996-2015	**2.5 [2.2;2.9]**				
Men	1.32	2.59	**3.1 [2.7;3.5]**	1996-2015	**3.1 [2.7;3.5]**				
Women	2.64	4.55	**2.4 [2.0;2.7]**	1996-2015	**2.4 [2.0;2.7]**				
Prevalence by age group**									
25-34	0.68	1.82	**4.7 [3.7;5.6]**	1996-2007	**7.7 [6.4;9.1]**	2007-2015	0.6 [-0.9;2.1]		
35-44	0.70	2.21	**5.5 [4.3;6.7]**	1996-2011	**4.5 [3.6;5.4]**	2011-2015	**9.5 [4.3;15.0]**		
45-54	1.55	3.14	**4.0 [3.3;4.8]**	1996-2011	**3.4 [2.8;4.0]**	2011-2015	**6.5 [3.2;10.0]**		
≥ 45	3.68	7.42	**2.8 [2.5;3.2]**	**1996-2015**	**2.8 [2.5;3.2]**				
≥ 45 Males	2.53	5.64	**3.9 [3.6;4.3]**	**1996-2015**	**3.9 [3.6;4.3]**				
≥ 45 Females	5.26	9.03	**2.4 [2.0;2.7]**	**1996-2015**	**2.4 [2.0;2.7]**				
55-64	2.96	5.60	**3.0 [2.6;3.4]**	1996-2015	**3.0 [2.6;3.4]**				
65-74	6.08	8.97	**1.7 [1.3;2.2]**	1996-2015	**1.7 [1.3;2.2]**				
75-84	7.80	13.9	**2.6 [2.0;3.2]**	1996-2007	**3.6 [2.7;4.5]**	2007-2015	**1.2 [0.2;2.1]**		
≥ 85	6.27	15.0	**3.0 [2.4;3.5]**	1996-2015	**3.0 [2.4;3.5]**				
Incidence									
Total	0.42	0.38	-0.5 [-1.4;0.5]	1996-2006	**-2.6 [-4.0;-1.1]**	2006-2015	**1.9 [0.4;3.5]**		
Men	0.27	0.26	-0.2 [-1.4;1.1]	1996-2006	**-2.5 [-4.4;-0.5]**	2006-2015	**2.5 [0.5;4.5]**		

Women	0.58	0.49	-0.5 [-2.4;1.4]	1996-1999	**-8.7 [-16.2;-0.6]**	1999-2013	-0.4 [-1.2;0.5]	2013-2015	11.8 [-3.3;29.3]
≥ 45	0.79	0.69	0.0 [-1.4;1.4]	1996-2011	-1.3 [-2.2;-0.3]	2011-2015	4.7 [-1.5;11.4]		
≥ 45 Males	0.44	0.51	0.6 [-0.4;1.6]	1996-2015	0.6 [-0.4;1.6]				
≥ 45 Females	1.11	0.81	-1.9 [-3.7;0]	1996-1999	-11 [-21.4;0.7]	1999-2015	0.0 [-0.9;-0.8]		

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval

* These percentages are standardized for the total Flemish population.

** Standardization was possible for the total population, but not for specific age cohorts.

*** Joinpoint regression modelling was used to estimate (A) APC in prevalence and incidence trends. Three possible trends were calculated during the 20-year study period.

Statistically significant differences for (A) APC are indicated in bold.

Table 2. Trends in multimorbidity of patients with knee osteoarthritis in the Intego registry (1996-2015).

Variables	1996-2000		2001-2005		2006-2010		2011-2015*		p-value **
Mean age (± SD)	55.3	(21.9)	57.6	(20.5)	57.8	(19.8)	56.9	(19.8)	0.384
Women, n (%)	972	(65%)	1234	(65%)	1419	(64%)	1412	(62%)	0.05224
Incidence, n	1503		1912		2202		2288		
Multimorbidity, n (%)									
Hypertension	359	(24%)	485	(25%)	623	(28%)	593	(26%)	0.0756
Diabetes	93	(6%)	161	(8%)	252	(11%)	346	(15%)	<0.001
CV events	323	(21%)	480	(25%)	597	(27%)	614	(27%)	<0.001
GI complication (ulcer)	28	(2%)	60	(3%)	59	(3%)	61	(3%)	0.3585
Renal failure	23	(2%)	70	(4%)	71	(3%)	66	(3%)	0.1025
Depression	141	(9%)	230	(12%)	259	(12%)	287	(13%)	0.009
Obesity	74	(5%)	101	(5%)	145	(7%)	191	(8%)	<0.001
Osteoporosis	57	(4%)	81	(4%)	107	(5%)	103	(5%)	0.2303
Cancer	29	(2%)	60	(3%)	59	(3%)	61	(3%)	<0.001
Asthma	125	(8%)	205	(11%)	328	(15%)	392	(17%)	<0.001
Substance abuse	4	(0%)	22	(1%)	31	(1%)	48	(2%)	<0.001
Disease burden, n (± SD)* **	1.63	(1.81)	1.84	(2.00)	2.18	(2.20)	2.34	(2.35)	<0.001

Legend:

Multimorbidity was measured for all incident cases with knee OA (i.e. at the time when knee OA was registered as a diagnosis).

*** Four time intervals of five years were defined to evaluate trends for all incident patients with knee osteoarthritis.**

**** *P-value* for multimorbidity was calculated with the Cochran-Armitage trend test; p-value for age was calculated with the Jonckheere-Terpstra trend test.**

***** The full list of diseases to calculate this mean disease burden is presented in supplementary file 2.**

Table 3. Trends in medication use of patients with knee osteoarthritis in the Intego registry (1996-2015).

Group/ Medication	Prev. in 1996	Prev. in 2015	Overall trend	Trend 1		Trend 2		Trend 3¥	
			AAPC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]	Years	APC [95% CI]
Acetaminophen	5.3	19.2	**6.7 [5.6-7.7]**	1996-2010	**8.0 [6.8-9.2]**	2010-2015	**3.1 [0.3;5.9]**		
Males	5.2	17.4	**5.8 [4.9-6.6]**						
Females	5.4	20.2	**7.0 [5.8-8.3]**	1996-2010	**8.7 [7.3;10.1]**	2010-2015	2.7 [-0.6;6.0]		
Oral NSAID (exclusion cox-2)	28.4	29.4	0.0 [-1.1;1.1]	1996-2002	-1.0 [-3.5;1.6]	2002-2008	2.4 [-0.1;5.0]	2008-2015	-1.2 [-2.4;0.1]
Males	28.6	28.8	0.5 [-0.2;1.2]	1996-2009	**1.1 [0.4;1.9]**	2009-2015	0.5 [-0.2;1.2]		
Females	28.3	29.6	0.3 [-0.1;0.8]						
Cox-2 selective NSAID	3.0	2.3	-7.7 [-36.0; 33.0]	2000-2004	-2.7 [-29.3;33.9]	2004-2007	-48.4 [-93.5; 309.5]	2007-2015	11.8 [-3.4;29.5]
Males	2.2	1.8	**-13.3 [-19.3;-6.7]**						
Females	3.4	2.7	-7.3 [-34.0;30.1]	2000-2004	-3.3 [-29.1;32.0]	2004-2007	-47.2 [-92.2; 257.6]	2007-2015	12.0 [-2.9;29.2]
Topical NSAID	7.8	5.9	-1.0 [-2.4; 0.4]	1996-2003	**-4.7 [-8.1;-1.2]**	2003-2015	1.2 [-0.0;2.4]		
Males	9.3	5.8	-0.9 [-2.2;0.5]						
Females	7.1	5.9	-0.8 [-2.3;0.7]	1996-2003	**-4.3 [-8.0;-0.4]**	2003-2015	1.3 [-0.0;2.6]		
Weak opioids	2.8	6.1	**4.0 [0.9;7.3]**	1996-1998	**36.3 [0.4;85.2]**	1998-2009	-0.9 [-2.3;0.5]	2009-2015	**4.0 [1.6;6.4]**
Males	1.5	5.2	**2.9 [1.5;4.4]**						
Females	3.3	6.7	2.8 [-0.0;5.7]	1996-2000	**14.7 [1.6;29.4]**	2000-2008	-3.2 [-6.4;0.2]	2008-2015	**3.5 [0.6;6.4]**
Strong opioids	2.5	4.3	1.9 [-0.4;4.3]	1996-2003	**9.0 [2.5;16.0]**	2003-2015	**-2.0 [-3.7;-0.3]**		
Males	1.7	3.6	-0.2 [-2.0; 1.6]						
Females	2.9	4.7	**2.3 [0.3;4.3]**	1996-2003	**10.0 [4.4;15.9]**	2003-2015	**-2.0 [-3.4;-0.5]**		
Parenteral glucocorticoids	9.1	8.1	-0.7 [-1.8;0.5]	1996-2005	**-2.1 [-3.5;-0.7]**	2005-2012	**2.7 [0.8;4.7]**	2012-2015	-4.1 [-9.2;1.2]
Males	8.1	8.6	**0.8 [0.0;1.6]**						
Females	9.6	7.9	**-1.3 [-2.6; 0.0]**	1996-2003	**-3.8 [-6.0;-1.5]**	2003-2012	**2.0 [0.6;3.4]**	2012-2015	-5.1 [-10.7;0.8]
Glucosamine*	0.6	1.8	**8.6 [2.4;15.1]**	2001-2004	**64.1 [25.0;115.3]**	2004-2011	**-9.6 [-14.3;-4.4]**	2011-2015	9.8 [-0.6:21.2]
Males	0.1	1.8	17.3 [-18.8; 69.5]	2001-2003	212.4 [-83.1;5664.3]	2003-2015	-0.4 [-4.8;4.2]		
Females	0.9	1.8	**6.8 [0.4;13.7]**	2001-2004	**56.7 [18.3;107.5]**	2004-2011	**-10.0 [-15.3;-4.3]**	2011-2015	8.2 [-3.6;21.4]

Legend:

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval; Prev., prevalence

***glucosamine: registration starts from 2001; cox-2 selective NSAID starts from 2000**

Bold: indicates that the (A)APC is significantly different from zero at the alpha= 0.05 level

¥= three possible time trends were computed with the joinpoint regression analysis. The corresponding time cohorts and APC are mentioned in these three columns

Figure 1.

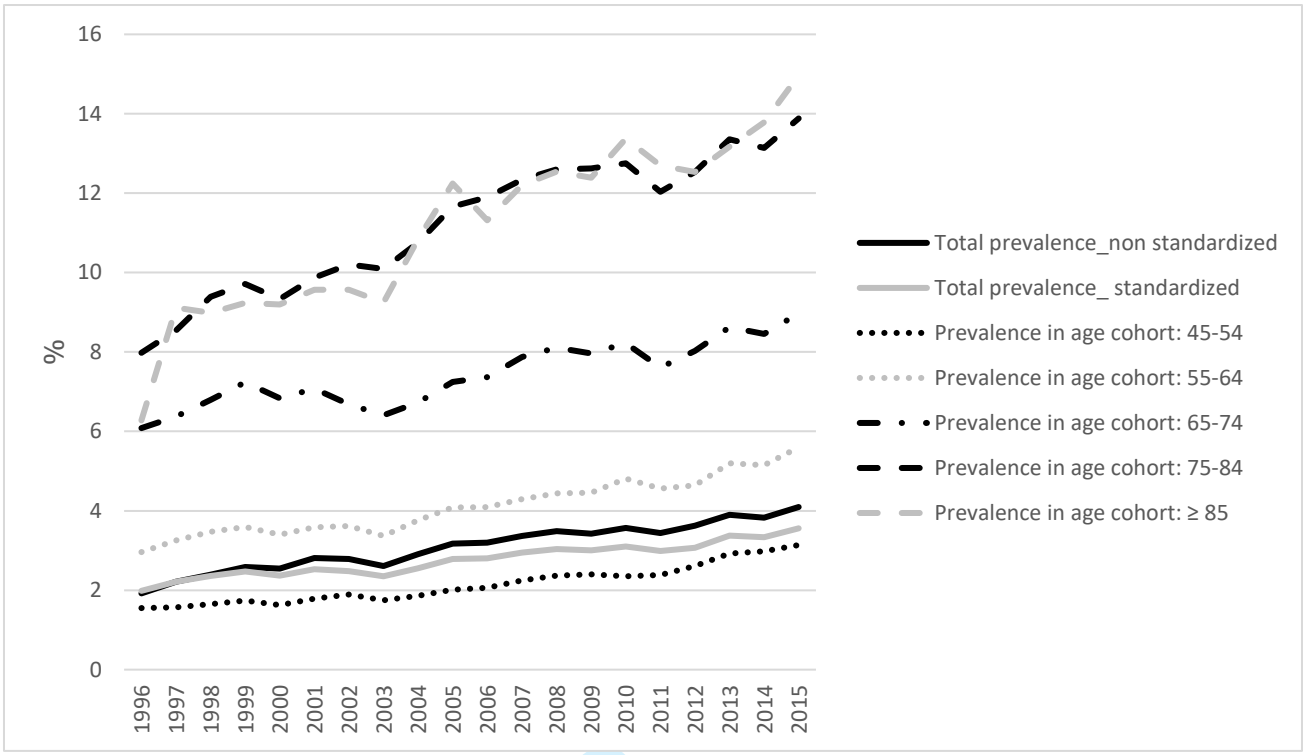


Figure 2.

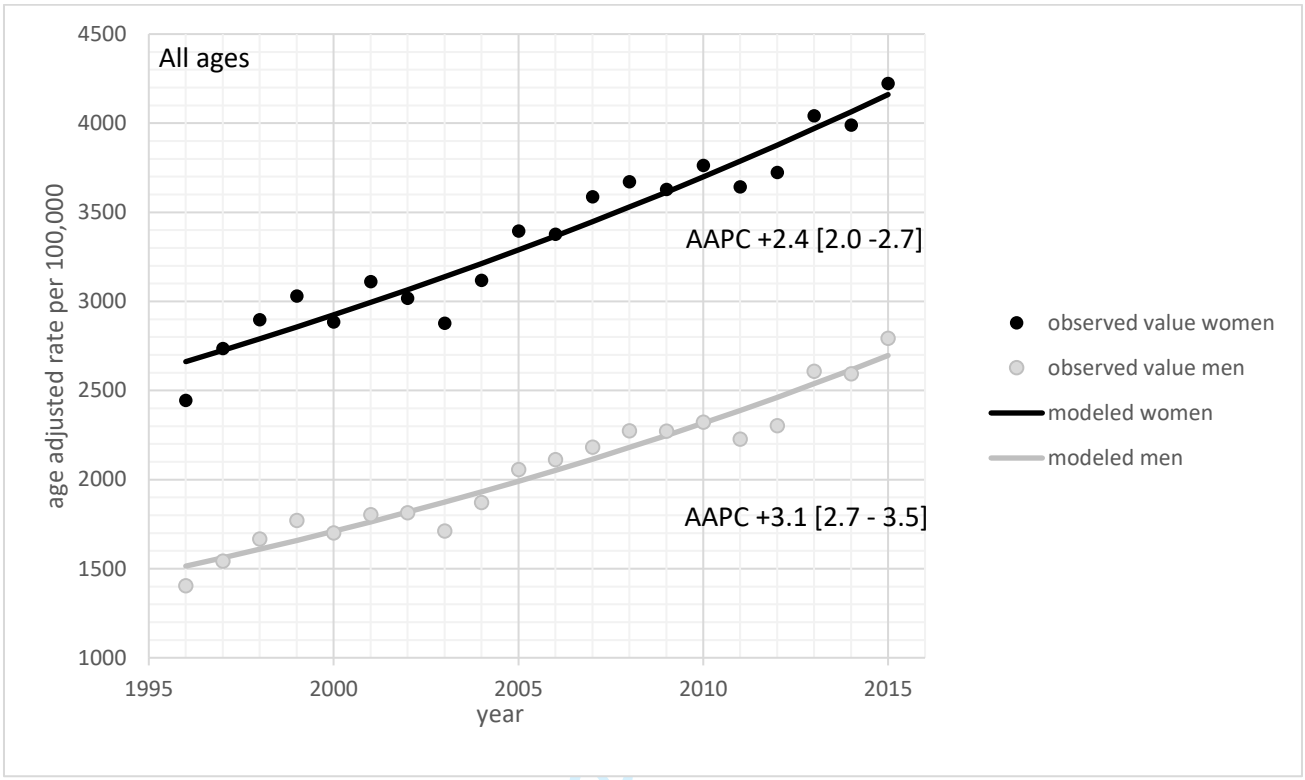
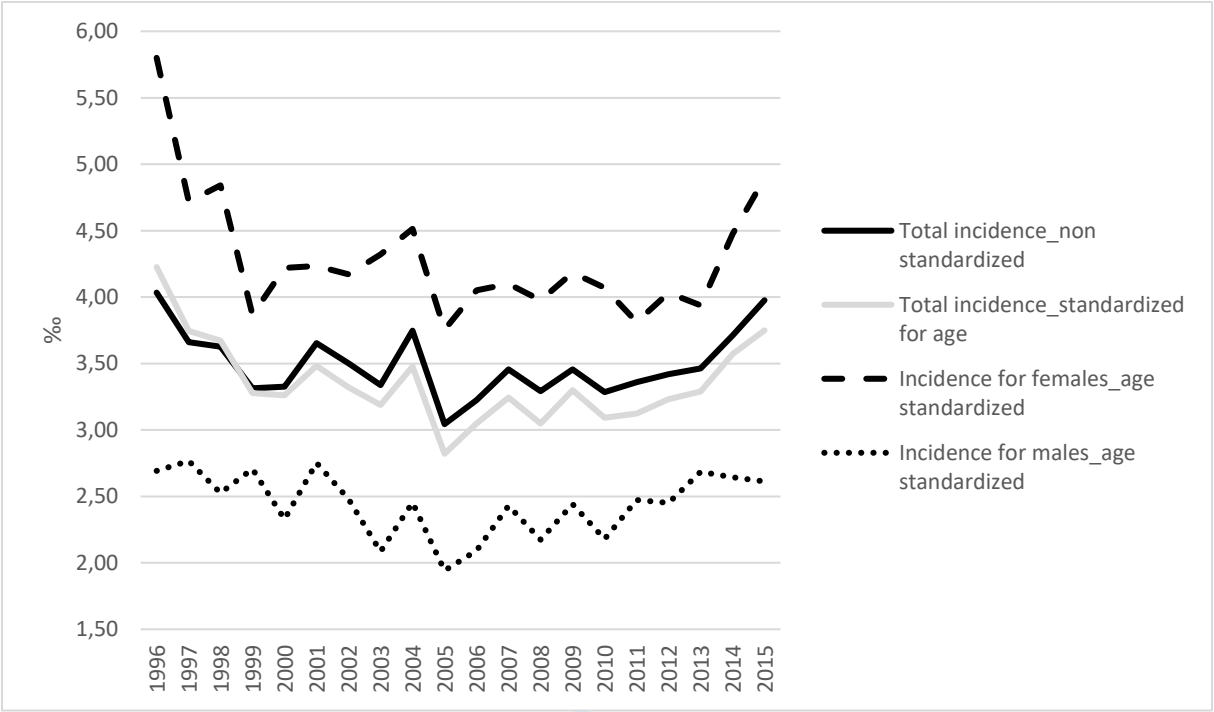
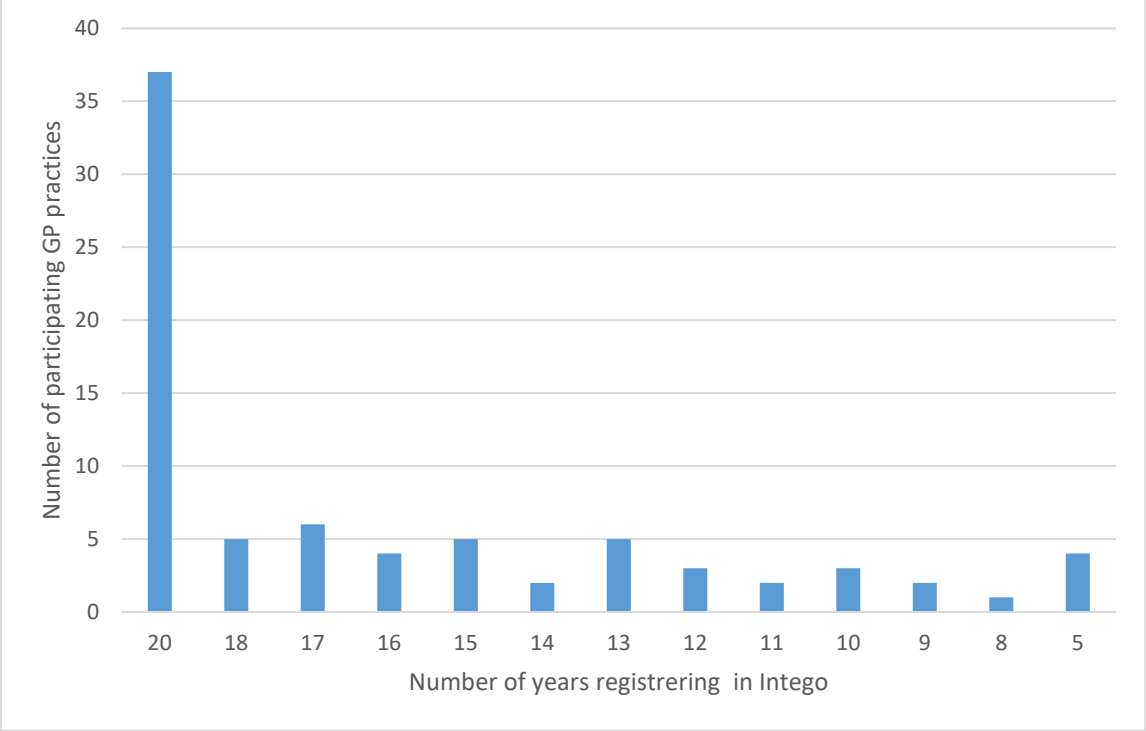


Figure 3.



Supplementary file 1. Participation of GP practices in Intego (1996-2015)



Supplementary file 2. ICPC codes and description of codes for the disease count

Codes to measure the disease count

The combination of the following 92 ICPC-2 codes were used to measure the disease count. If codes are not mutually exclusive (e.g. T89 and T90), then they count for one.

ICPC code	Description
A79	Malignancy NOS
A90	Congenital anomaly OS/multiple
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B78	Hereditary haemolytic anaemia
B83	Purpura/coagulation defect
B90	HIV-infection/aids
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
F83	Retinopathy
F84	Macular degeneration
F94	Blindness
H83	Otosclerosis
H84	Presbyacusis
H86	Deafness
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K82	Pulmonary heart disease
K86	Hypertension uncomplicated
K87	Hypertension complicated
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L88	Reumatoãde arthritis
L89	Osteoarthrosis of hip
L90	Osteoarthrosis of knee
L91	Osteoarthrosis other
L95	Osteoporosis
L98	Acquired deformity of limb
N70	Poliomyelitis
N74	Malignant neoplasm nervous system
N85	Congenital anomaly neurological

N86	Multiple sclerosis
N87	Parkinsonism
N88	Epilepsy
N89	Migraine
N90	Cluster headache
N92	Trigeminal neuralgia
P15	Substance abuse: chronic alcohol
P28	Limited function/disability (p)
P70	Dementia
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P77	Suicide/suicide attempt
P79	Phobia/compulsive disorder
P80	Personality disorder
P85	Mental retardation
P98	Psychosis NOS/other
R79	Chronic bronchitis
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R95	Chronic obstructive pulmonary disease
R96	Asthma
S77	Malignant neoplasm of skin
S87	Dermatitis/atopic eczema
S91	Psoriasis
S97	Chronic ulcer skin
T71	Malignant neoplasm thyroid
T80	Congenital anom endocrine/metab.
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U04	Incontinence urine
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
W72	Malignant neoplasm relate to preg.
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malign neoplasm male genital other
Y85	Benign prostatic hypertrophy

Other ICPC codes used in this manuscript

ICPC code	description
P17	Substance abuse: tobacco
P19	Substance abuse: drug abuse
L89	Osteoarthritis of the hip
L90	Osteoarthritis of the knee
L91	Osteoarthritis of other locations (other than knee/hip)

ICPC codes used with Intego software to define multimorbidity

Definition of cancer

Intego uses a set of 22 ICPC-2 codes to define cancer as a multimorbidity: A79, B73, B72, B74, D74, D75, D76, D77, L71, N74, R84, R85, T71, U75, U76, U77, W72, X75, X76, X77, Y77, and Y78.

Definition of substance abuse

Intego uses a combination of three ICPC-2 codes to define substance abuse: P15, P 17, and P19.

Supplementary file 3. ACT coding for pharmacological agents used in the management of knee osteoarthritis.

	ACT coding
Acetominophen	N02BE01
Oral NSAID (exclusion cox-2 selective)	M01AB M01AC-M01AE M01AG
COX-2 selective NSAID	M01AH
Topical NSAID	M02AA
Glucosamine supplements	M01AX05
Chondroitin supplements	M01AX25
Hyaluronic acid	M09AX01
Weak opioids	N02AX02 N02AJ01 N02AJ02 N02AJ03 N02AJ06 N02AJ07 N02AJ08 N02AJ09 N02AJ13 N02AJ14 N02AJ15
Strong opioids	N02AA N02AB N02AC N02AD N02AE N02AF
Glucocorticoids	H02AB

Supplementary file 4. Number of people in the yearly contact group (by gender and age cohort) in Intego (1996-2015)

Year	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Yearly contact group	83011	81763	85940	86535	95932	90973	106664	125202	120962	128251
Total prevalence knee osteoarthritis*	1595 (1.92)	1809 (2.21)	2055 (2.39)	2236 (2.58)	2439 (2.54)	2554 (2.81)	2973 (2.79)	3268 (2.61)	3516 (2.91)	4069 (3.17)
By gender										
Male	39648	38927	40796	41252	45478	43325	50857	59759	57700	61446
Female	43363	42836	45144	45283	50454	47648	55807	65443	63262	66805
By age cohort										
≤ 24 year	23732	23712	24493	24206	25165	24237	29108	34424	32142	34294
25-34 year	14859	13322	13741	13243	14185	12899	14699	17477	16617	17538
35-44 year	13919	13462	14123	14240	16502	14404	16189	19282	18303	19040
45-54 year	9993	10315	11193	11599	13405	12812	14933	17469	17199	18450
55-64 year	8107	8148	8633	8675	9798	9729	11704	13731	13754	14826
65-74 year	7266	7357	7755	8027	9121	8943	10488	11961	11950	12247
75-84 year	3797	3955	4367	4694	5559	5785	7097	8218	8414	8900
≥ 85 year	1338	1492	1635	1851	2197	2164	2446	2640	2583	2956

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yearly contact group	133931	132322	134733	140259	140126	151971	127717	130398	131651	123261
Total prevalence Knee osteoarthritis*	4284 (3.20)	4454 (3.37)	4695 (3.48)	4798 (3.42)	5003 (3.57)	5223 (3.44)	4635 (3.63)	5081 (3.90)	5041 (3.83)	5049 (4.09)
By gender										
Male	64012	63472	64423	67305	67075	72892	60829	62541	63404	58841
Female	69919	68850	70310	72954	73051	79079	66888	67857	68247	64420
By age cohort										
≤ 24 year	35769	35655	36210	38384	38014	41116	34065	35626	35673	33736
25-34 year	18551	18311	18916	20113	20003	21668	18264	18804	19578	17818
35-44 year	19640	18767	18672	19137	18627	19883	16597	16865	17434	15937
45-54 year	19379	19220	19595	20210	20345	22093	17972	18207	18220	16950
55-64 year	15512	15636	16054	16523	16827	18570	15657	15827	16037	15415
65-74 year	12372	12135	12108	12347	12363	13780	11505	11567	11494	11169
75-84 year	9305	9214	9439	9694	9835	10388	9070	8938	8601	8140
≥ 85 year	3403	3384	3739	3851	4112	4473	4587	4564	4614	4096

Legend:

***(%) = proportion of patients with knee osteoarthritis. This proportion describes the data from the Intego registry and is not standardized for the total Flemish population.**

Supplementary file 5. Demographic characteristics of patients with knee osteoarthritis in Intego registry (1996, 2005, and 2015).

	1996***		2005		2015	
	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized	n/N	% Non-standardized vs standardized
Prevalence, gender						
Total	1.595/83011	1.92; 1.99	4069/128251	3.17;2.79	5049/123261	4.09; 3.56
Men	518/39648	1.31; 1.32	1348/61446	2.20;1.97	1817/58841	3.09; 2.59
Women	1077/43363	2.48; 2.64	2721/66805	4.07;3.67	3232/64420	5.02;4.55
Prevalence, age cohorts**						
≤ 24	172	1.59	307	1.89	232	1.56
25-34	101	0.68	272	1.55	324	1.82
35-44	98	0.70	225	1.18	353	2.22
45-54	155	1.55	372	2.01	532	3.13
55-64	240	2.96	606	4.08	863	5.60
65-74	442	6.08	887	7.24	1002	9.00
75-84	303	7.98	1038	11.66	1130	13.9
≥ 85	84	6.28	362	12.24	613	15.0
Incidence, gender						
Total	325/81416	0.40; 0.42	378/124182	0.30;0.28	470/118212	0.40; 0.38
Men	102/39130	0.26; 0.27	129/60098	0.21;0.19	167/57024	0.29; 0.26
Women	223/42286	0.53; 0.58	249/64084	0.39;0.38	303/61188	0.50;0.49

Legend:

N=yearly contact group: the number of patients that visited their general practitioner at least once during once year

***the first % refers to the age-specific data from the Intego register; the second % is the standardized Intego data for the total Flemish population.**

**** Standardization was possible for the total population, but not for specific age cohorts.**

***** Data are available for 20-year period. In this table 10-year interval periods are described.**

The RECORD statement

Checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Title (Title page and abstract) 1.2 Geographic region: abstract 1.3 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, p.2, paragraph 1-4
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, p.2, paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, p. 3, design

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods, pp. 3-4, design and data collection
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1 Methods, p. 3, supplementary file 3 for the ICPC codes and supplementary file 4 for the ACT codes 6.2 Intego registry external validation described in Truyers et al. Reference 6.3 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1 Methods, p. 3, design, supplementary file 1 till 4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Page 5: Methods, design pp. 3-4, the Intego

		Describe comparability of assessment methods if there is more than one group			Database is explained in detail
Bias	9	Describe any efforts to address potential sources of bias			Methods, design, p.3 and Discussion, pp. 11-12, paragraph 5
Study size	10	Explain how the study size was arrived at			NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods, data analysis p.5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			(a) methods, data analysis p.5 (b) NA (c) NA (d) NA (e) NA
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the	12.1 Data sharing statement, p.14

				investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2 Availability of data and materials, p.14
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	NA
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Results, pp. 6-9 Table 1 Figures 1-3 (b) NA (c) NA

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			(a) Results, pp. 6-9 Table 1-3 Figures 1-3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			NA
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion, last paragraph with conclusions p.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Discussion, paragraph 5, pp. 11-12

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, pp. 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, pp. 10-12
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Funding, p.14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials, p.14

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.