Explaining declining hip fracture rates in Norway: a population-based modelling study

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The Lancet Regional Health - Europe 2023;30: 100643

Published Online xxx https://doi.org/10.1016/j.lanepe.2023.100643

Summary

Background Although age-standardised hip fracture incidence has declined in many countries during recent decades, the number of fractures is forecast to increase as the population ages. Understanding the drivers behind this decline is essential to inform policy for targeted preventive measures. We aimed to quantify how much of this decline could be explained by temporal trends in major risk factors and osteoporosis treatment.

Methods We developed a new modelling approach, Hip-IMPACT, based on the validated IMPACT coronary heart disease models. The model applied sex- and age stratified hip fracture numbers and prevalence of pharmacologic treatments and risk/preventive factors in 1999 and 2019, and best available evidence for independent relative risks of hip fracture associated with each treatment and risk/preventive factor.

Findings Hip-IMPACT explained 91% (2500/2756) of the declining hip fracture rates during 1999–2019. Two-thirds of the total decline was attributed to changes in risk/preventive factors and one-fifth to osteoporosis medication. Increased prevalence of total hip replacements explained 474/2756 (17%), increased body mass index 698/2756 (25%), and increased physical activity 434/2756 (16%). Reduced smoking explained 293/2756 (11%), and reduced benzodiazepine use explained (366/2756) 13%. Increased uptake of alendronate, zoledronic acid, and denosumab explained 307/2756 (11%), 104/2756 (4%) and 161/2756 (6%), respectively. The explained decline was partially offset by increased prevalence of type 2 diabetes and users of glucocorticoids, z-drugs, and opioids.

Interpretation Two-thirds of the decline in hip fractures from 1999 to 2019 was attributed to reductions in major risk factors and approximately one-fifth to osteoporosis medication.

Funding The Research Council of Norway.

Keywords: Hip fractures; Osteoporosis; Public health; Epidemiology; Epidemiologic methods

Introduction

Osteoporotic fractures cause serious morbidity, disability, reduced quality of life and excess mortality, with hip fracture being the most severe, accounting for the majority of health care expenditures, mortality, and morbidity.[1] In Europe, lifetime risk of hip fracture at age 50 years was comparable to that of stroke in Europe for both women (20%) and men (14%).[2]

Declining age-adjusted hip fracture rates have been observed in Europe and North America, however, with the increased life expectancy and growth of the population aged >60 years, the number of fractures is forecast to exceed what can be offset by the declining age-specific incidence.[3,4] Understanding the drivers behind these trends is essential to counter the future hip fracture burden on healthcare and society. The introduction of pharmacological osteoporosis treatments cannot fully explain the decreasing hip fracture rates.[5] Secular lifestyle changes such as reduced smoking, increased body mass index (BMI), and physical activity have been suggested,[6] however, their relative quantitative contributions remain unclear.

We have previously shown that the age-adjusted hip fracture rates declined by 27% in Norway during

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Research in context

Evidence before this study

We searched PubMed using the terms «hip fracture», «incidence», «secular trend*», and «time trend*» for studies published between 2000 and 2020. Overall, studies showed that age-adjusted hip fracture rates have declined in Europe and North America in recent decades, however, the drivers behind these trends remain unclear.

Added value of this study

To our knowledge, this is the first study to model the combined relative contributions of secular changes in risk factor levels and treatment uptake on hip fracture trends. The model applies the best available evidence for age- and sex-specific magnitudes of relative risks and relative risk reductions associated with risk/preventive factors and pharmacological treatments. Our findings show that two-thirds of the decline in hip fracture rates observed in Norway was explained by changes in population risk factor levels, while one-fifth was attributed to uptake of osteoporosis medication. Knowledge about the relative contributions of risk factor changes and treatment uptake is important for informing public health recommendations and policy changes to contain the forecast hip fracture burden.

Implications of all the available evidence

With the increased life expectancy and growth of the population aged >60 years, the number of hip fractures is forecast to exceed what can be offset by the declining age-specific incidence. Our results show that most of the decline could be explained by factors not directly relating to hip fracture prevention and point to substantial missed opportunities in osteoporosis treatment. There is considerable potential in pharmacological fracture-preventive treatment, e.g., through implementing fracture liaison services, to reduce the future hip fracture burden. In addition, most of the reduction in hip fracture rates occurred in the oldest old, however, data on risk factor levels, medication uptake, and relative risks are sparse in this population and highlight the need for including this age group in future studies.

1999–2019.[7] In the present study, we aimed to quantify the relative contributions of osteoporosis treatment and secular changes in risk factors to the observed decline in hip fracture incidence in Norway 1999–2019.

Methods

Modelling and data sources

We developed a novel model, Hip-IMPACT, based on the validated IMPACT coronary heart disease model methods.[8–10] Hip-IMPACT applies prevalence of risk/preventive factors and pharmacological treatments at two time points and their population attributable risks to quantify their contributions to the observed change over time in hip fracture incidence (Supplementary Appendix, Section A).

We explored the literature for modifiable risk factors for which there is an established causal relationship with hip fracture, preferably randomised controlled trials (RCTs) and meta-analyses (Supplementary Appendix, Section B). Candidate variables were not included in the final model if their causal role is not settled, or if they are considered a mediator on the causal pathway of another variable included in the model, such as bone mineral density (BMD), see the directed acyclic graph (DAG) in the Supplementary Appendix, Fig. B1.1. In addition, for a risk/preventive factor to have an impact on the hip fracture trend, there must have been a change in prevalence of the factor over the period. The candidate variables should have acceptable available estimates to indicate prevalence within sex and age strata in Norway in 1999 and 2019. The variables in the final model included pharmacological treatments for osteoporosis (alendronate, zoledronic acid, and denosumab), preventive factors including total hip replacements (which practically eliminate the risk of fracturing the operated hip), BMI > 25, physical activity, and risk factors including current smoking, type 2 diabetes, and drugs affecting BMD and/or fall risk (glucocorticoids, opioids, benzodiazepines used for anxiety and insomnia, and z-drugs (non-benzodiazepine hypnotics) used for insomnia). A number of other variables were considered but ultimately not included. A description of the variable selection is available in the Supplementary Appendix, Section B.

Prevalence of risk/preventive factors and treatments in 1999 and 2019 were obtained from population-based health surveys and national registries, including the Norwegian Prescription Database (NorPD), Statistics Norway, The Norwegian Arthroplasty Register, and the literature. The Norwegian Prescription Database (NorPD) (http://www.norpd.no/) was established in 2004 and contains detailed data on dispensed drugs in all outpatient pharmacies in Norway but does not cover institutions such as hospitals and nursing homes. Statistic Norway's periodic Living Conditions Survey (www.ssb.no/en/statbank/table/06181/) covers a wide range of information on living conditions and health on a national representative selection of persons. The Norwegian Arthroplasty Register (https://helse-bergen.no/nasjonal-kompetansetjeneste-for-leddproteser-og-hoftebrudd/norwegian-national-advisory-unit-on-arthroplasty-and-hip-fractures) was established in 1987 and records new prostheses and subsequent revisions.

When more than one data source was available, we chose the source considered to be most representative in the sense that it would cover the entire population and/or include stratified information on sex and age groups. In the case of unavailable prevalence data for 1999 and/or 2019, we used regression to extrapolate the prevalence based on the available data (see details in Supplementary Appendix, Section C).

Fully adjusted relative risks and corresponding 95% confidence intervals (CI) were obtained from the literature, preferably from RCTs and meta-analyses, or from large cohort/registry studies if RCTs and meta-analyses were not available. Detailed information about relative risks and data sources can be found in the Supplementary Appendix, Section D.

Hip fractures prevented

The study covered the population of Norway aged 50 years and older in 1999 and 2019. Population size as of 1 January 1999 and 1 January 2019 by sex and five-year age groups (50 through 90+) was available in official population tables published by Statistics Norway (www.ssb.no/en). Information on all hip fractures treated in hospitals in Norway in 1999 and 2019 was available in the Norwegian Epidemiologic Osteoporosis Studies hip fracture database (NORHip), including up to two hip fractures per person.[7] NORHip has been validated and shown high agreement with quality-checked data obtained from medical records in hospitals (www.norepos.no/documentation).

We calculated the expected number of hip fractures in 2019 given unchanged hip fracture rates since 1999 by multiplying the age- and sex specific 1999 rates by the population size in each five-year age stratum in 2019, thus accounting for the ageing of the population. The difference between the observed and expected numbers in 2019 represented the number of prevented hip fractures that the model would have to explain.

Osteoporosis treatment

Hip fractures prevented in 2019 explained by osteoporosis medication was calculated by multiplying the number of users of each medication group by the hip fracture rate in untreated osteoporosis patients[11] and by their relative risk reduction (Supplementary Appendix, Section A2.3).

Hip fractures prevented = number of users × relative risk reduction × hip fracture rate.

The number of users, hip fracture rates in untreated osteoporosis patients, and the relative risk reduction due to treatment, all stratified by sex and five-year age groups, were obtained from the NorPD and/or derived from published sources (Supplementary Appendix, Section C2, D2, and Section E).

As alendronate was on the market in 1999, we calculated the net benefit over the period by subtracting the prevented hip fractures explained by alendronate in 1999 from prevented hip fractures explained by alendronate in 2019. We divided alendronate users into high-, medium- and low-compliance users based on medication possession ratio (MPR). The MPR was calculated as the ratio of the number of days a patient had their medicine on hand (based on the sum of defined daily doses filled in the pharmacy) to the number of days a patient was eligible to have the medicine on hand, in line with previous studies.[12] High-compliance users (MPR $\geq$0.8) were assumed to obtain full treatment effect as reported in clinical trials. Medium-compliance users ($0.5 \leq$ MPR < 0.8) were assumed to obtain half of the treatment effect, while low-compliance users (MPR <0.5) were assumed to have negligible treatment effect and were disregarded.[13] For zoledronic acid (annual infusion) and denosumab (bi-annual injection) we assumed 100% compliance.[14] We assumed no overlap in treatments and a negligible number of patients who switched treatment in 2019 and thus counted twice.

Changes in risk- and protective factors

Based on population-attributable risk fraction (PARF), we estimated the effect of changes in the prevalence of current smoking, physical activity (>1 h/week), high BMI (>25 kg/m^2), type 2 diabetes, use of drugs with side effects on BMD (glucocorticoids) or fall risk (benzodiazepines, z-drugs, opioids), and total hip prostheses. PARF was calculated as $(P \times (RR-1))/(P \times (RR-1) + 1)$, where P is risk factor prevalence and RR is its associated relative risk of hip fracture. The number of prevented hip fractures was then estimated as the expected number of hip fractures in 2019 multiplied by the difference between PARF in 1999 and that in 2019 (Supplementary Appendix, Section A2.4). For some variables the calculated prevented hip fractures were negative, implying an estimated increased number of hip fractures attributed to the change in prevalence of that variable.

Hip fractures prevented = Expected hip fractures in 2019 (given unchanged hip fracture rates since 1999) × ($PARF_{1999}$—$PARF_{2019}$).

Prevalence estimates, relative risks, and hip fracture rates in the general population are available in the Supplementary Appendix (Section C3, C4, D3, D4, and E).

Cumulative risk reduction and model fit

The model input is based on fully adjusted relative risk estimates. However, hip fractures occur as a consequence of multiple risk factors which are often interrelated. Cohort studies and meta-analyses generally do not provide joint estimates of overlapping risk factors but independent relative risk estimates. Benefits attributable to risk factors which may be causally related, or which overlap in population groups, should thus not be combined by simple addition. We therefore calculated the cumulative risk reduction, which accounts for risk factor prevalence overlap but assumes independence of

effects. The equation for risk factors is stated as:

$$CR = 1 - \left((1 - R_{BMI}) \times \left(1 - R_{smoking}\right) \times (1 - R_{diabetes}) \right.$$

$$\left. \times \ldots \times (1 - R_n)\right)$$

where R denotes the risk factor change attributable to a specific risk factor.

The additive risk-reduction (AR) was calculated as $AR = (R_{BMI}) + (R_{smoking}) + (R_{diabetes}) + \ldots + (R_n)$.

We first calculated the (additive) hip fractures prevented attributed to risk factor change. These were then adjusted down by the ratio:

Adjustment factor = CR/AR.

Total prevented hip fractures explained

The hip fractures prevented explained by each treatment and risk/preventive factor change were summed and compared with the observed changes in hip fracture rates by sex and five-year age groups. Unexplained hip fractures prevented in the overall model were presumed to be attributable to uncertainties in our calculated estimates or to unmeasured risk factors.

Sensitivity analyses

We implemented a multiple way, probabilistic sensitivity analysis using Monte Carlo simulation in Ersatz version 1.3 (http://www.epigear.com). This add-in allows probabilistic bootstrapping in Excel by repeated random draws from specified distributions for input variables (Supplementary Appendix, Table G1.1) and then calculates the 95% uncertainty intervals from the realised values of the output variable (hip fractures prevented). We calculated 95% uncertainty intervals based on 1000 draws.

Ethics

This modelling study was principally based on aggregated data from published sources that are cited in the manuscript and Supplementary Appendix. Some data, including hip fracture counts, medication possession ratio for oral anti-osteoporosis medication, prevalence of use of oral glucocorticoids, and relative risks for hip fracture by BMI levels were obtained from a research project with linked individual-level registry data. The study and data linkages have been approved by the Regional Committee for Medical and Health Research Ethics (REC South East A, ref 15538), the Norwegian Institute of Public Health, the Norwegian Directorate of Health, Statistics Norway, and the Norwegian Data Protection Authority. The data have been handled in accordance with the General Data Protection Regulation, and a Data Protection Impact Assessment has been conducted. Based on the Norwegian Act on medical and health research (the Health Research Act), the Regional Committee for Medical and Health Research Ethics has granted exemption from confidentiality for the linked data sources that are not consent-based.

Role of the funding source

The study was funded by The Research Council of Norway, grant number 275270. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

A total of 9309 hip fractures were recorded in 1999 and 9121 in 2019. Expected number of hip fractures in 2019 given unchanged rates was 11,877, i.e., an additional 2756 fractures. Hip-IMPACT explained 91% (2500 hip fractures) of the gap between the expected and observed number in 2019. Under the assumptions of the sensitivity analysis, the minimum and maximum number of hip fractures explained by the model were 1915/2756 (70%) and 3065/2756 (111%), respectively. Fig. 1 shows the number of hip fractures prevented by each treatment and risk/preventive factor.

Contributions from changes in treatment uptake

An estimated 575/2756 (21%) of prevented hip fractures were attributable to increased uptake of osteoporosis medication, Table 1. Increased alendronate uptake explained 307/2756 (11%) of the decline, while 104/2756 (4%) was attributed to zoledronic acid and 161/2756 (6%) to denosumab.

Contributions from changes in risk factor levels

An estimated 1822/2756 (66%) of prevented hip fractures were attributable to risk factor changes, Table 2. Increased prevalence of people living with hip prostheses explained 474/2756 (17%) of the hip fractures prevented, while 698/2756 (25%) were attributable to increased BMI, and 434/2756 (16%) to increased physical activity. The decline in smoking was estimated to prevent 293/2756 (11%) hip fractures. Increased prevalence of type 2 diabetes contributed an additional 77 hip fractures (–3%).

Contributions from changes in usage of drugs with side effects

An estimated 366/2756 (13%) hip fractures prevented were attributed to reduced benzodiazepine use over the period. However, this was partly offset by increased usage of glucocorticoids, z-drugs, and opioids which contributed additional 150 (–5%), 32 (–1%) and 78 (–3%) hip fractures, respectively, Table 3.

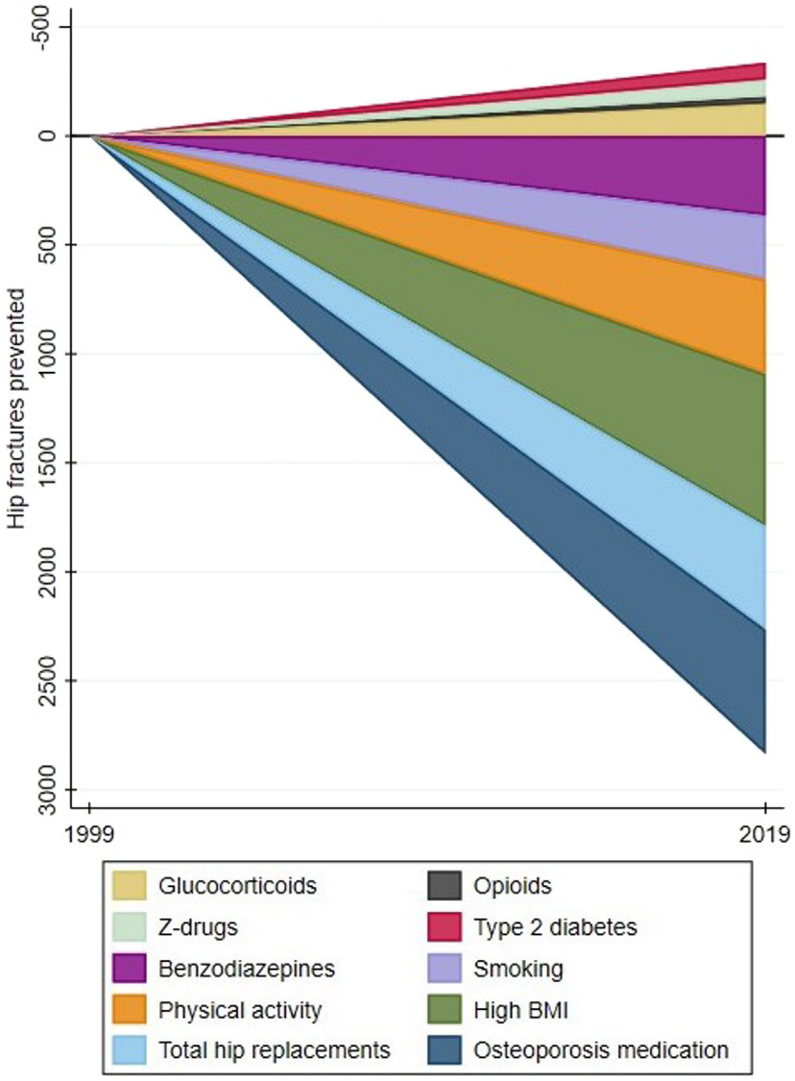

Fig. 1: **Number of hip fractures prevented* by changes in pharmacological osteoporosis treatment, risk factors and preventive factors in the Norwegian population between 1999 and 2019.** *Some risk factor changes (type 2 diabetes and use of glucocorticoids, opioids and z-drugs) increased the number of hip fractures over the period (represented with a negative integer).

Discussion

To the best of our knowledge, this is the first study to quantify the impact of population-level changes in treatment uptake and risk factors on hip fracture incidence. In this nationwide study utilising our newly developed Hip-IMPACT model, we found that time trends in major risk and preventive factors accounted for more than two-thirds of the observed decline in hip fracture, whereas osteoporosis medication explained approximately one-fifth of the decline. Although hip fracture rates have declined significantly in recent decades,[7] the ageing population forecasts an increasing societal hip fracture burden that is unlikely to be offset by declining hip fracture rates.[15] Knowledge about the relative contributions of risk factor changes and treatment uptake is important for informing public health recommendations and policy changes to further contain the large future fracture burden.

Contribution of osteoporosis medication

The modest contribution of osteoporosis medication was not surprising. In line with our findings, increased uptake of osteoporosis medication in Denmark during 2005–2015 explained up to 20% of the decline in a best-case scenario.[5] As the fracture-preventive treatment effect applied in Hip-IMPACT was based on clinical trials rather than real-world data, the calculations may have

Treatment	Number of patients 1999	Number of patients 2019	Relative risk reduction	Number of fractures prevented			Proportion explained of total hip fractures prevented		
				Best estimate	Minimum estimate	Maximum estimate	Best estimate	Minimum estimate	Maximum estimate
Alendronate, high-compliance (MPR[a] ≥ 0.8)									
Women	11,860	31,972	–	213	163	253	8%	6%	9%
Men	1268	5921	–	69	52	82	2%	2%	3%
Total	13,128	37,893	0.53	282	215	335	10%	8%	12%
Alendronate, medium-compliance (0.5 ≤ MPR[a] < 0.8)									
Women	2222	5990	–	19	17	20	1%	1%	1%
Men	225	1052	–	6	5	6	<1%	<1%	<1%
Total	2447	7042	0.25	25	22	26	1%	1%	1%
Zoledronic acid									
Women	–	11,632	–	88	69	104	3%	2%	4%
Men	–	1572	–	16	12	19	1%	<1%	1%
Total	–	13,204	0.41	104	81	123	4%	3%	4%
Denosumab									
Women	–	10,238	–	151	89	197	5%	3%	7%
Men	–	674	–	10	6	13	<1%	<1%	<1%
Total	–	10,912	0.40	161	95	210	6%	3%	8%
Total	–	–	–	**572**	**413**	**694**	**21%**	**15%**	**25%**

The HIP-IMPACT Model. [a]Medication possession ratio (MPR) was calculated as the ratio of the number of days a patient had their medicine on hand (based on the sum of defined daily doses filled in the pharmacy) to the number of days a patient was eligible to have the medicine on hand.

Table 1: **Estimated number of hip fractures prevented by pharmacological osteoporosis treatment in women and men in Norway, 2019.**

yielded a generous estimate of prevented hip fractures explained by alendronate treatment. In contrast, the contribution from zoledronic acid may be underestimated[16] as data on pharmacological treatment given in nursing homes and hospitals, e.g., as part of fracture liaison services, are not available in the NorPD.[16] The Norwegian Capture the Fracture Initiative (NoFRACT), a large multi-centre study on secondary fracture prevention conducted 2015–2019, is expected to have increased the uptake of zoledronic acid in Norway.[17] Comparison of NorPD with the Norwegian Drug Wholesale Statistics has shown that only 4% of all dispensed anti-osteoporosis drugs were not registered in the NorPD, but the number may be much higher for zoledronic acid.[16] To reduce the likelihood of underestimating zoledronic acid use, we retrieved the number of users in NorPD and doubled this number for all sex- and age groups.

Our results support the body of literature pointing to substantial missed opportunities in osteoporosis treatment for fracture prevention. Large treatment gaps have been identified across Europe; of an estimated 21 million European women eligible for osteoporosis treatment in 2019, 15 million women were untreated corresponding to an average treatment gap of 71%.[1] From 2010 to 2019, total direct costs of hip fracture increased by 64%, while pharmacological costs decreased from 5% to 3%.[1] Evidence show that osteoporosis medications reduce fracture risk when targeted appropriately,[18] and that such initiatives are cost saving.[19] Our results, in light of the treatment gap, suggest considerable potential in pharmacological fracture-preventive treatment, e.g., through implementing fracture liaison services that have shown to improve treatment uptake and reduce fracture incidence.[20]

Contribution of risk factor changes

Approximately two-thirds of the hip fractures prevented were attributed to changes in risk factor levels. Increased population BMI explained the majority, particularly in men. A non-linear relationship between BMI and hip fracture risk has been observed. Whereas a low BMI has been associated with increased risk, fracture risk seems to level off at BMI 25 or higher.[21,22] The prevalence of high BMI increased in all sex- and age groups, reflecting a shift in the population distribution that resulted in a lower proportion of underweight persons. These results confirm that low body weight is an important modifiable risk factor.

As previously described,[7] the increased prevalence of persons living with total hip prostheses explained almost one-fifth of the decline. A total hip replacement practically eliminates the risk of fracturing the operated hip and is associated with a RR of 0.5 for a future hip fracture (see Supplementary Appendix, Section B2.2.5).[7] The proportion of the decline that could be attributed to hip replacements was higher in women compared to men, as a larger proportion of women undergo a hip replacement and live longer.[23]

Risk/preventive factor	Absolute levels of risk factors		Change in risk factor levels		Relative risk	Number of fractures prevented			Proportion explained of total hip fractures prevented		
	1999	2019	Absolute change	Relative change (%)		Best estimate	Minimum estimate	Maximum estimate	Best estimate	Minimum estimate	Maximum estimate
BMI > 25											
Women	55.8	62.6	6.7	12.0	0.63	388	336	445	14%	12%	16%
Men	59.9	74.6	14.7	24.6	0.67	310	259	370	11%	9%	13%
Total	57.7	68.4	10.7	18.6	–	698	595	815	25%	22%	30%
Physical activity (exercise > 1 h/week)											
Women	50.0	73.0	23.0	46.1	0.87	310	216	399	11%	8%	14%
Men	53.1	70.7	17.6	33.2	0.87	124	93	160	4%	3%	6%
Total	51.4	71.9	20.5	39.9	–	434	309	559	16%	11%	20%
Smoking											
Women	22.4	12.0	−10.4	−49.5	1.30	145	118	172	5%	4%	6%
Men	27.6	13.1	14.5	52.6	1.47	148	128	167	5%	5%	6%
Total	24.8	12.5	−12.3	−49.5	–	293	246	339	11%	9%	12%
Type 2 diabetes											
Women	5.0	6.7	1.7	33.7	1.27	−37	−45	−31	−1%	−2%	−1%
Men	6.4	10.1	3.7	58.7	1.27	−40	−47	−33	−1%	−2%	−1%
Total	5.6	8.4	2.7	48.3	–	−77	−92	−64	−3%	−3%	−2%
Total hip replacements											
Women	5.1	7.4	2.3	45.6	0.5	396	363	430	14%	13%	16%
Men	2.4	3.8	1.4	58.8	0.5	78	70	87	3%	2%	3%
Total	3.8	5.6	1.8	46.7	–	474	433	517	17%	16%	19%
Total	–	–	–	–	–	**1822**	**1491**	**2166**	**66%**	**54%**	**79%**

The HIP-IMPACT Model.

Table 2: **Estimated number of hip fractures prevented attributed to changes in population risk/preventive factors in women and men in Norway, 2019.**

Increased proportion of physically active individuals in the population explained 16% of the decline in hip fracture rates. Physical activity may postpone age-related bone loss[24] and increase muscle strength and balance.[25] We used a conservative measure of a minimum of 1 h exercise per week, which may not be unreasonable as any level of activity appears to be protective compared to sedentary behavior.[24,26]

Smoking prevalence declined over the period and explained 11% of hip fractures prevented. Smoking is associated with lower weight and BMD. On the other hand, the prevalence of type 2 diabetes increased over the period and contributed an additional 77 hip fractures according to our model.

Contribution of changes in usage of drugs with side effects

The net effect of changes in usage of drugs with side effects explained 4% of the decline in hip fracture rates. The variation was large, with some drugs increasing and some reducing the hip fracture rates.

Increased use of glucocorticoids accounted for an additional 150 hip fractures. Our data do not adequately discriminate between long- and short-term use, nor the dosage used. We did, however, limit the risk of overestimating the impact of glucocorticoids by counting only those with at least two filled prescriptions within a calendar year. Considering the treatment gap in osteoporosis, administering osteoporosis medication needs to be a priority to counteract the negative effects of glucocorticoids on bone.

The usage of fall-risk increasing drugs varied across different drug types. The usage of benzodiazepines, often prescribed to reduce anxiety or insomnia,[16] decreased over the period and explained approximately 13% hip fractures prevented, while the usage of z-drugs, used for insomnia, was more varied; overall usage declined over the period but increased in men aged 90+ and in women aged 80+. This may reflect that guidelines recommend prescribing z-drugs over benzodiazepines.[16] Although the use of opioids and z-drugs did not contribute a large number of additional hip fractures, these findings highlight the importance of assessing extensive drug consumption in the elderly.

Unexplained decline

Approximately one-tenth of the decline in hip fracture rates could not be explained by the Hip-IMPACT model. Some may be explained by residual confounding and variables we were unable to include in the model (Supplementary Appendix, Section B). Moreover, age-period-cohort analyses have suggested the presence of significant birth cohort effects on hip fracture rates.[27] Early life course factors such as childhood nutrition[28]

Drugs with side effects	Absolute levels of risk factors		Change in risk factor levels		Relative risk	Number of fractures prevented			Proportion explained of total hip fractures prevented		
	1999	2019	Absolute change	Relative change (%)		Best estimate	Minimum estimate	Maximum estimate	Best estimate	Minimum estimate	Maximum estimate
Glucocorticoids											
Women	3.2	4.9	1.7	52.7	1.37	−100	−114	−87	−4%	−4%	−3%
Men	2.3	3.9	1.7	73.5	1.37	−50	−57	−44	−2%	−2%	−2%
Total	2.8	4.4	1.6	59.6	–	−150	−171	−131	−5%	−6%	−5%
Benzodiazepines											
Women	13.6	6.6	−7.0	−51.5	1.5	277	267	287	10%	10%	10%
Men	6.9	3.5	−3.4	−49.4	1.5	89	85	94	3%	3%	3%
Total	10.6	5.1	−5.5	−51.7	–	366	352	381	13%	13%	14%
Z-drugs											
Women	21.3	17.9	−3.4	−15.8	1.9	−91	−113	−66	−3%	−4%	−2%
Men	11.2	9.0	−2.2	−19.3	1.9	59	51	69	2%	2%	2%
Total	16.7	13.6	−3.1	−18.4	–	−32	−62	3	−1%	−2%	<1%
Opioids											
Women	18.5	18.7	0.1	0.7	1.54	−63	−86	−39	−2%	−1%	−3%
Men	14.1	14.9	0.8	6.0	1.54	−15	−22	−9	−1%	<−1%	<−1%
Total	16.5	16.8	0.4	2.2	–	−78	−108	−48	−3%	−2%	−2%
Total	–	–	–	–	–	**106**	**11**	**205**	**4%**	**<1%**	**7%**

The HIP-IMPACT Model. [a]Some risk factor changes (type 2 diabetes and use of glucocorticoids, opioids and z-drugs) increased the number of hip fractures over the period (represented with a negative integer).

Table 3: **Estimated hip fractures prevented[a] attributed to changes in usage of drugs with side effects in women and men in Norway, 2019.**

and healthy ageing may explain some of the decline. Grip strength, a biomarker of current and future health has improved in younger cohorts in Norway[29] and has been associated with lower hip fracture risk.[30]

Several widely studied potential risk factors for hip fracture acting through BMD or fall risk have not been included in the Hip-IMPACT model, due to insufficient evidence for their causal effect on hip fracture or absence of valid and comparable prevalence data in age strata for 1999 and 2019. In addition, factors for which the prevalence has not changed or has changed very little over time, and exposures with a very low prevalence, would be expected to have a negligible contribution to the calculated number of prevented hip fractures in the model.

We were unable to comprehensively account for potential temporal changes in fall risk. Several modifiable risk factors, including drugs with side effects on bone and fall risk, have been identified but for many the association with hip fracture remains unclear. Although fall prevention programs have been shown effective in reducing fall risk, their effect on hip fractures have largely been inconclusive. Furthermore, many such programs include physical activity, which we have included in the model.[31]

The association between alcohol intake and hip fracture is complex (see Supplementary Appendix, Section B3.1.7). Over the past decades, an increasing proportion of older Norwegians drinking alcohol has been observed, particularly among older women. In addition, the older population drink more frequently, however, most drink relatively few alcohol units (1–2), and a corresponding increase in risky drinking has not been observed.[32] How this level of consumption may affect BMD and the risk of falls, ensuing hip fracture, remains unclear.

Nutritional status also affects fracture risk through BMD and fall risk. A sufficient energy and protein intake to maintain a healthy weight, expressed by BMI in our model, is important for maintaining bone integrity, muscle strength and functional level to prevent fractures in older age. Other nutritional factors acting on bone health, of which vitamin D supplementation is the most widely studied, may indeed have changed in the population over time, but systematic reviews including a vast number of RCTs show no effect of vitamin D supplementation alone on fracture risk.[33]

Strengths and limitations

A major strength of the present study is the use of national registry data and population surveys to estimate prevalence. The Norwegian setting uniquely offers registry data covering the total population and nationally representative survey data, and therefore is an ideal setting for understanding the drivers of the hip fracture trends in populations. Replicating the model in other countries will be important to assess whether similar contributions of explanatory factors can be identified in

other countries with declining age-adjusted hip fracture rates.

A policy model like Hip-IMPACT stands in contrast to a multivariate regression model for determining causal relationships of a risk/preventive factor or treatment with an outcome. Where a multivariate regression model represents a statistical approach for obtaining specific associations in a single data set, a policy model such as Hip-IMPACT seeks to integrate and synthesise the best available estimates from a variety of sources to reliably estimate the extent to which a range of factors, acting in combination, explain or predict a population outcome. The model incorporates the best coefficients from the published literature (meta-analyses, RCTs, if available) for the reduction in hip fracture risk attributed to time trends in pharmacological treatment or the independent effect sizes of change in each risk factor on hip fracture risk. However, the Hip-IMPACT model did not include all possible risk- and preventive factors, highlighting significant knowledge gaps. Most of the reduction in hip fracture rates occurred in the oldest old,[7] however, data on risk factors are sparse in these age groups. Prevalence estimates and relative risks could often not be granulated to five-year age groups and were sometimes unavailable for the oldest old (Supplementary Appendix, Section C and D).

There is measurement error associated with all inputs in the model. We implemented stochastic uncertainty analysis in Excel using Ersatz, which showed that the results were robust. We also calculated the cumulative risk reduction, reducing the likelihood of double counting prevented hip factors due to overlap of risk factor prevalence. Overall, lag times between the change in the risk factor rate and the change in the event rate were not modelled and it was assumed that these lag times would be negligible over a period of two decades. As with all models attempting to capture complex and interacting changes, it remains possible that there were additional (unquantifiable) sources of error not captured by the uncertainty analysis.

In conclusion, our Hip-IMPACT model showed that two-thirds of the decline in Norwegian hip fractures from 1999 through 2019 could be attributed to reductions in major risk factors while one-fifth could be explained by uptake of osteoporosis medication. With the increased life expectancy and growth of the population aged > 60 years, the results suggest that there is large potential in pharmacological fracture-preventive treatment, to contain the future hip fracture burden.

Contributors

MOF, GST, HEM, and KH developed the original idea. GST, HEM, and KH acquired the funding for study. MOF and HKK designed and implemented the model with inputs from HEM, KH, and BA. KH and HKK analysed and prepared individual-level data. All authors had access to the Excel spreadsheet with aggregate-level data used in the model and interpreted the results. HKK wrote the first draft of the manuscript, and all authors revised the work for intellectual content and approved the final version to be published and accept responsibility for the decision to submit for publication.

Data sharing statement

Corresponding Author KH may be contacted for information about the data and materials. This study was principally based on aggregate-level data available in published literature cited in the manuscript and Supplementary Appendix. The individual-level data used to inform some of the background data, presented in the Supplementary Appendix, are available upon application to the respective data owners (Norwegian Institute of Public Health, Norwegian Directorate of Health, and Statistics Norway). Legal restrictions apply to the availability of these data, which were used under approval for the purpose of the study, and so are not publicly available.

Declaration of interests

BA declares institutional research contracts with UCB and Novartis, consulting fees from UCB and Kyowa-Kirin, and speakers fees from UCB, Amgen, Pharmacosmos, Gedeon Richter, and Eli Lilly. All other authors declare no conflicts of interest.

Acknowledgements

The authors thank the members of the NOREPOS network for valuable scientific discussions concerning conceptualisation and development of the Hip-IMPACT model. The study was funded by The Research Council of Norway, grant number 275270. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funder and no endorsement is intended nor should be inferred. Information from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Directorate of Health is intended nor should be inferred.

Funding: This work was supported by a grant from the Research Council of Norway.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100643.

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