An Epidemiologic Study on Hand Osteoarthritis in Peri-to-Postmenopausal Women

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Dekan

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Contents

Summary

Osteoarthritis is a slowly developing chronic joint disease mainly characterized by joint pain and nodes with no curative treatment available except for joint replacement. The etiology of osteoarthritis is not exactly known, but the hypothesis that osteoarthritis not only evolves from wear-and-tear but is also inherent to systemic components is widely accepted. Systemic inflammation as in obesity or dyslipidemia was shown to negatively influence osteoarthritis of non-weight bearing joints such as joints in the hands. Hand osteoarthritis develops frequently in postmenopausal women. Menopausal transition in women mainly occurs from age 45 to 54, involves changes in sex hormones, and is associated with vasomotor and genitourinary symptoms mainly treated with systemic and vaginal hormone replacement therapy, respectively. Further associated symptoms such as joint pain or osteoarthritis (symptomatically treated with painkillers) or increased lipid levels (mainly treated with statins to reduce the risk of a cardiovascular event) are less known to the general public but carry a high disease burden.

By means of epidemiologic studies using women's primary care health records in the United Kingdom, this thesis aimed to help find drugs potentially delaying hand osteoarthritis onset by describing and assessing drugs treating symptoms evolving in menopausal transition in association with hand osteoarthritis. Potential negative associations may result in a decreased burden of this incurable disease.

In a first descriptive study, we described incidence rates of hand osteoarthritis and of hormone replacement therapy use in women aged 40 to 69 years. We observed that rates of hormone replacement therapy initiation and of new diagnoses of hand osteoarthritis behaved inversely over time and uniformly in 5-year age groups between 40 to 54 years but not in older age groups. Hormone replacement therapy initiation rates shaped in a skewed Gaussian curve with a tail in older age groups while onset of hand osteoarthritis plateaued from age 55. In a second nested case-control study, observing women from age 45 longitudinally, we assessed the association between systemic hormone replacement therapy initiation and hand osteoarthritis overall and in women with recorded menopause only as recorded menopause was a major confounder. Most hand osteoarthritis cases

occurred shortly after menopause, therefore, we assessed the timing of hormone replacement therapy initiation relative to menopause in current users as well as of hormone replacement therapy cessation relative to hand osteoarthritis diagnoses in past users, compared to non-users. The association between hormone replacement therapy use and hand osteoarthritis yielded an increased risk of hand osteoarthritis of 32%. However, in women with recorded menopause, the risk of hand osteoarthritis in hormone replacement therapy users disappeared compared to non-users. Furthermore, we observed a 28% decreased risk of hand osteoarthritis if hormone replacement therapy was initiated around menopause and used continuously, compared to non-users. This potential beneficial effect diminished the later hormone replacement therapy was initiated. However, we also observed a statistically non-significant 25% increased risk of hand osteoarthritis shortly after therapy cessation. In a third cohort study, in women aged 45 to 64 years, we assessed the association between statin initiation and hand osteoarthritis and between statin initiation and generalized osteoarthritis (i.e. multiple joints affected, hand osteoarthritis is usually part of generalized osteoarthritis), overall, stratified by age, and by pre-existing dyslipidemia. Furthermore, we used psoriasis and tinnitus as negative control outcomes to control for confounding by differential menopause onset (psoriasis) and healthcare seeking behavior (psoriasis, tinnitus). We observed that statin use was neither associated with hand osteoarthritis nor with generalized osteoarthritis irrespective of age or pre-existing dyslipidemia. The use of negative control outcomes corroborated this finding.

Our results support the existing hypothesis that menopause is a risk factor of hand osteoarthritis. However, it is likely not the only risk factor for hand osteoarthritis because otherwise we would have expected hand osteoarthritis incidence rates to decline similarly to those of hormone replacement therapy use among older age groups. Furthermore, our results suggest that timely initiation of hormone replacement therapy relative to menopause may be crucial for a potential delay of hand osteoarthritis onset to at least after hormone replacement therapy cessation. Finally, our results suggest that the lipid lowering effect of statins does not seem to translate into a reduced risk of hand osteoarthritis in peri-to-postmenopausal women.

Abbreviations

OA	osteoarthritis
UK	United Kingdom
IR	incidence rate
py	person-years
TNF	tumor necrosis factor
IL	interleukin
MMP	matrix metalloproteinase
NICE	National Institute for Health and Care Excellence
MRI	magnet resonance imaging
EULAR	European League Against Rheumatism
TC	total cholesterol
LDL	low-density lipoprotein
TG	triglycerides
HRT	hormone replacement therapy
CVD	cardiovascular disease
HDL	high-density lipoprotein
CPRD	Clinical Practice Research Datalink
BMI	body mass index
GP	general practitioner
OR	odds ratio
HIV	human immunodeficiency virus
AIDS	acquired immune deficiency syndrome
IMD	index of multiple deprivation
CI	confidence interval
PS	propensity score
HR	hazard ratio
EB	entry block
WHI	Women's Health Initiative

Introduction

1 Introduction

1.1 Hand osteoarthritis

1.1.1 Disease manifestation

Osteoarthritis (OA) is a slowly developing chronic joint disease that presents as a heterogeneous disorder.[1] It can affect any joint in the body and several joints at the same time. If multiple joints are affected, the disease is called “generalized OA”, but the term lacks a standard definition.[2] If the disease localizes in certain joints of the hand, it is referred to as hand OA. Typically, hand OA is also present in patients who are diagnosed with generalized OA.[2] Hand OA neither has a uniform definition but can be considered an umbrella term of multiple types of OA that manifest in the hand: In “interphalangeal OA”, distal and proximal interphalangeal joints are affected. If nodes are present in distal or proximal interphalangeal joints, called Heberden and Bouchard nodes, respectively, the disease is also referred to as “nodal OA”.[1] Furthermore, in “base of thumb OA” the carpometacarpal joint of the thumb is affected, also called *first carpometacarpal joint*.[1] Figure 1 depicts affected joints. OA in metacarpal joints of the wrist is not considered part of hand OA, but is called wrist OA.

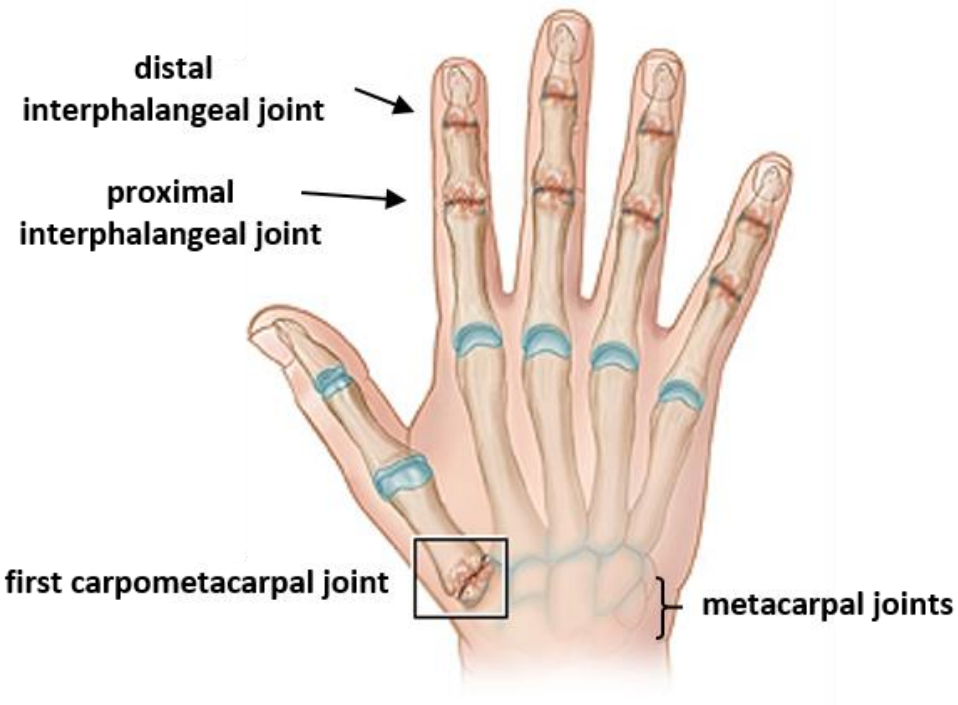

Fig1. In hand osteoarthritis, distal and proximal interphalangeal joints as well as the first carpometacarpal joint may be affected
Adapted from https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=zm6124, accessed Jan 4, 2019

There may be clustering of affected joints in hand OA, which, if occurring, occurs primarily by row and symmetrically in both hands with patterns being similar among women and men.[3,4] In around one forth to one third of patients, multiple joint types of the hand are affected (i.e. distal/proximal interphalangeal joints, first carpometacarpal joint).[3,5] Reported prevalence of affected joint types vary between studies but distal interphalangeal joints generally seem to be most frequently affected.[3–5] In affected joints, patients may experience activity-related pain, stiffness, decreased grip strength, and, in later stages, impaired mobility, and eventually, disability.[1] By means of imaging techniques, the following structural abnormalities may be seen in affected joints: osteophytes (bone spurs), joint space narrowing, subchondral sclerosis (increased bone density underneath the cartilage), loss of cartilage, bone cysts, and subluxation (incomplete joint dislocation).[1,6,7] However, not all patients who have structural abnormalities (i.e. OA diagnosed by medical imaging, also referred to as "radiographic OA") have OA symptoms (also referred to as "symptomatic OA" which is clinically relevant), and vice versa.[8,9] The research community is divided over the course of the disease but it is generally suggested to progress with time.[10]

1.1.2 Epidemiology

OA is a highly prevalent disease. According to the "Osteoarthritis in General Practice" report of *Arthritis Research UK*, around one third of inhabitants of the United Kingdom (UK) aged 45 years and older (around 8.8 million) have sought medical advice for OA between 2004 and 2010.[11] Thereof, around 1.56 million patients (corresponding to approximately 6% of UK inhabitants) have sought medical advice for hand or wrist OA.[11] Women were almost three times more likely to seek medical advice for hand or wrist OA than men if aged 45-64 (8% and 3%, respectively) and almost twice more likely if aged 65-74 (9% and 5%, respectively).[11]

The rate of disease onset (incidence rate, IR) of hand OA was described to be 4.3 per 1'000 person-years (py, age- and sex-standardized) in UK general practice in 2013.[12] Age-specific IRs of hand OA in women from the year 2000 in the UK show that disease onset peaks between age 55 and 60 at around 4/1'000 py and decreases slowly subsequently.[12] IRs of hand OA were reported to be higher in women than in men until the age of 85 when both populations show similar rates at around 2/1'000 py (IR of hand OA in men have plateaued at this rate as of age 65).[12] Once set on, hand OA cannot be cured and manifests as a moderately prevalent disease in postmenopausal women and the elderly.[13] End-stage hand OA results in

high morbidity as it prevents people from performing everyday activities such as dressing, writing/typing, or preparing a meal.[11]

Main risk factors for primary hand OA (idiopathic hand OA due to multifactorial/unknown causes) include postmenopausal age in women and older age in general,[13,14] genetic predisposition (family history),[14] metabolic syndrome,[15] visceral fat (in men),[16] obesity,[14,16] and to a lesser extent handedness and occupations associated with constant repetitive hand movements.[17]

1.1.3 Etiology

The exact etiology of primary hand OA is unknown. Mechanical pressure is of major influence for weight-bearing joints (e.g. knee, hip), but less applicable to non-weight bearing joints (e.g. finger, thumb).[15] Hence, hand OA was suggested to be a systemic disease associated with systemic factors.[9,18] On a biochemical level, it was reported that hand OA may be associated with cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 as part of concomitant inflammation of, for example, the metabolic syndrome[15,19] or single diseases thereof (e.g. obesity[20], hyperlipidemia[21,22]). OA development may therefore be due to "joint failure" referring to failing regular cartilage turnover in which the rebuilding process is hindered by the presence of cytokines. For example, presence of IL-1 in the synovial fluid inhibits the production of collagen, a major component of cartilage.[23] Furthermore, TNF[24] (secreted by T cells, mediating cartilage loss[25]), IL-1, and IL-6 are supposed to play a similar role in OA as they play in the inflammatory and cartilage degeneration process (i.e. synovitis) of rheumatoid arthritis. However, IL-6 (present in the synovium, secreted by chondrocytes and macrophages) was shown to have an ambivalent role in OA stimulating both degradation and building of cartilage.[26,27] Cartilage breakdown in OA was suggested to be carried out by enzymes called matrix metalloproteinases (MMP).[28] Osteophyte formation was reported to be enhanced by transforming growth factor-beta.[29] A scheme of involved factors and enzymes is depicted in Figure 2.

Hand OA is called "secondary" if causative factors including birth abnormalities, previous trauma, articular hypermobility, or other inflammatory arthropathies (mainly rheumatoid arthritis) are present at diagnosis.[1,7,30] However, the disease manifestation is the same as in primary hand OA.

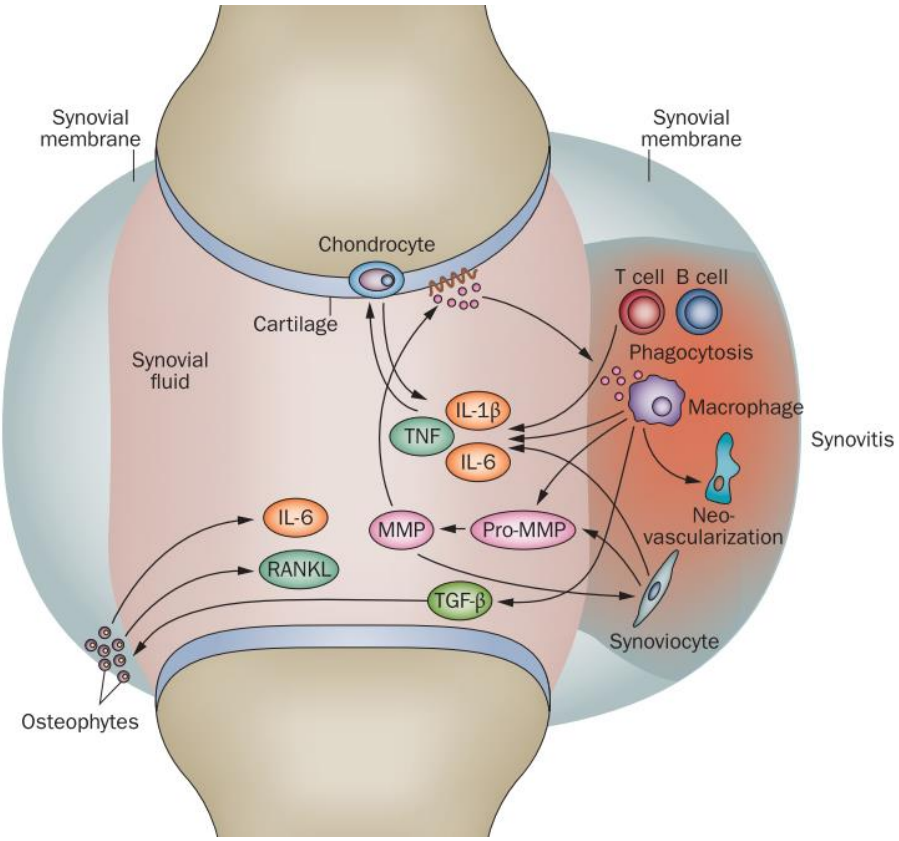

Fig2. Scheme of involved factors and enzymes in osteoarthritis
TNF: tumor necrosis factor, IL: interleukin, MMP: matrix metalloproteinase,
RANKL: receptor activator of nuclear factor κB ligand, TGF-β, transforming growth factor β.
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1.1.4 Diagnostic methods

According to the National Institute for Health and Care Excellence (NICE) guidance on "Osteoarthritis: care and management", the diagnosis of hand OA is carried out without further investigations if a patient is aged 45 years or older, shows activity-related joint pain, and has morning joint stiffness for less than 30 minutes (or no morning joint stiffness).[8] Other diagnostic methods include joint palpation to assess pain and tenderness, and imaging techniques such as radiographic assessment, ultrasonography, or magnet resonance imaging (MRI).[1,7,31]

Differential diagnoses of hand OA include hemochromatosis, rheumatoid arthritis, psoriatic arthritis, gout, and pseudogout.[32]

1.1.5 Therapeutic options

NICE guidance on "Osteoarthritis: care and management" suggests a holistic approach of non-pharmacological and top-up pharmacological treatment to ease OA symptoms as, to date, OA cannot be cured except through joint replacement.[8] Non-pharmacological treatment suggestions mainly target OA of large weight-bearing joints (i.e. hip, knee); suggestions include local muscle strengthening, weight loss, joint manipulation, and advice on appropriate footwear and walking aids.[8] Recommendations of the European League against Rheumatism (EULAR) focuses on the management of hand OA.[33] EULAR also recommends a combination of non-pharmacological and pharmacological treatment which should be individualized according to affected joints, presence of inflammation, and underlying structural abnormalities while education about joint protection and an exercise regimen are recommended for all hand OA patients.[33] NICE and EULAR agree that local pharmacological treatments (topical non-steroidal anti-inflammatory drugs or capsaicin) are preferable over systemic treatments (oral non-steroidal anti-inflammatory drugs, cyclo-oxygenase2 inhibitors, or opioids).[8,33] NICE and EULAR further agree that surgery such as joint replacement surgery should only be considered as a final treatment option when other treatments have failed.[8,33] EULAR recommends splints for base of thumb OA, but advises against general use of intra-articular corticosteroid injections in hand OA.[33] EULAR further recommends short-term oral glucocorticoid use but advises against the use of biologic agents such as TNF blockers or IL-1 receptor antagonists due to lack of efficacy in hand OA.[33]

1.2 Menopause

Menopause is defined as the point in time when a woman has ceased menstrual cycles for one entire year.[34,35] The menopausal transition period, also called perimenopause, starts with alterations of more than seven days from normal cycle length.[34] Menopause results from near depletion of ovarian follicles and hence reduced estrogen production.[36] This occurs either naturally during the 5th or 6th decade of a woman's life (median at around 50 years of age)[37,38] or can be surgically induced through bilateral oophorectomy and/or hysterectomy.[39] After menopause, a woman enters postmenopause.[34,35] In postmenopausal women, ovaries have ceased to produce estrogen, but aromatases[40] in non-gonadal sites throughout the body (e.g. adipose tissue, bone, brain, liver, blood vessels) continue to convert precursors into small quantities of estrogen.[41,42]

1.2.1 Postmenopausal symptoms

Postmenopausal symptoms are manifold, reflecting the various different locations of estrogen receptors throughout the body such as the reproductive system, brain, bone, liver, heart muscle, coronary arteries, and adipose tissue.[43,44] Principal symptoms include vasomotor symptoms (hot flushes, night sweats), which are most prevalent shortly after menopause, and genitourinary symptoms (vaginal atrophy, urinary tract infections), which were reported to be inversely associated with serum estrogen levels.[34] Notably, vasomotor symptoms do not necessarily correlate with serum estrogen levels,[34,45] which may be explained by altered local estrogen concentrations in the hypothalamus, for example, which regulates body temperature.[42] Further symptoms in postmenopausal women include sleep disturbance,[34] mood changes,[34,46] memory and concentration loss,[46] altered sexual function,[34,46] joint pain and OA,[46,47] osteoporosis,[34,46] and unfavorable changes in fat mass deposition (i.e. increase in central fat)[48–52] and in circulating lipids (increasing total cholesterol [TC], low-density lipoprotein [LDL], triglycerides [TG], and lipoprotein(a))[50,53,54]. Postmenopausal symptoms occur in up to 75-85% of women of whom around one fourth are affected by severe symptoms.[34,46,55] In the UK, around 40% of postmenopausal women were reported to seek medical advice because of postmenopausal symptoms.[55]

1.2.2 Vasomotor and genitourinary symptom control

NICE guidance on “Menopause: diagnosis and management” suggests the use of systemic hormone replacement therapy (HRT) to treat vasomotor symptoms during up to five years.[46] HRT consists of the synthetically produced hormones estrogen, progesterone, or derivatives thereof (e.g. tibolone). The mechanism of action of HRT is to replenish decreased estrogen and progesterone levels after menopause.[56] If a woman prefers non-hormonal therapy, drugs acting in the central nervous system such as antidepressants and antiepileptics, may also be used to lower vasomotor symptoms, but are not recommended by NICE guidance as first-line treatment.[46]

To alleviate genitourinary symptoms, NICE suggests the use of vaginal estrogen (if necessary on top of systemic formulations) as long as symptoms prevail.[46] Given evidence of associated risks of cardiovascular disease (CVD),[57,58] breast cancer,[59] and venous thrombotic events,[58] the choice of HRT formulation and dosage should depend on risk factors (e.g. age, lifestyle, family history of adverse events) and personal preferences after risk-benefit evaluations.[46,60]

1.2.3 Other symptom control

Other symptoms associated with menopause acknowledged with a treatment proposal by NICE guidance on "Menopause: diagnosis and management" are low mood (suggested to treat with HRT or cognitive behavioral therapy) and sexual difficulties (suggested to treat with HRT or testosterone).[46]

Joint pain and osteoarthritis

The International Menopause Society and the North American Menopause Society suggest that muscle and joint pain or stiffness (typical features of OA) may improve with HRT.[61–63] However, to date, no clear association could be established between OA and HRT.[62] Preclinical studies mainly assessed the effect of HRT on knee OA and yielded contradictory results.[64] Weight-bearing joints such as the knees are subject to mechanical pressure, a major risk factor of OA.[15] Therefore, hand OA is considered a more suitable outcome to assess the relationship between OA and systemic exposures such as drugs. Small observational studies (n ≤1'000) investigating the effect of HRT on hand OA respective generalized OA also yielded contradictory results.[65–69] In humans, HRT use was reported to reduce the concentration of a cartilage metabolite in the urine when compared to non-use,[70] but the potential beneficial effect of estrogen on joint tissues is not completely understood.[62] On a biochemical level, estrogen receptors are present in joint tissues[71,72] and estrogen was found to inhibit IL-6 resulting in chondrocyte proliferation[26]. Estrogen withdrawal was found to increase the production of TNF[24] and MMPs[73] involved in OA development and progression, and to increase the sensitivity of maturing osteoclasts to its activator ligand (*RANKL*, resulting in bone loss if secreted by osteoblasts, unknown activity if expressed in cartilage[74]).[24] To date, a potential effect of progesterone alone or in combination with estrogen on articular cartilage remains unknown. Estrogen depletion is discussed as a potential trigger factor of OA progression.[9,75]

Unfavorable changes in circulating lipids and fat mass deposition

Unfavorable changes in circulating lipids and fat mass deposition carry an inherent risk of CVD. It was reported that increased fat mass itself contributed to elevated lipid levels.[50] Furthermore, in a longitudinal study, lipid levels (TC, TG, LDL, and high-density lipoprotein [HDL]) were not only higher among peri-to-postmenopausal women compared to

premenopausal women, but also among HRT users compared to peri-to-postmenopausal non-users.[50] Other studies reported lower LDL and higher HDL levels in HRT users when compared to non-users[53] and the return of deviating levels of TC, LDL, HDL, and lipoprotein(a) to premenopausal levels with HRT[76]. The International Menopause Society and the North American Menopause Society state beneficial effects of HRT on lipid levels[62] and abdominal obesity[63], respectively. According to NICE guidance on "Cardiovascular disease: risk assessment and reduction, including lipid modification", statins (principal lipid lowering treatment) should be offered to patients for primary prevention of CVD after lifestyle changing engagement to tackle secondary causes of dyslipidemia (i.e. smoking, alcohol consumption, hypertension, obesity).[77] However, menopause as a potential trigger factor of increased lipid levels is not mentioned in NICE guidance on "Cardiovascular disease: risk assessment and reduction, including lipid modification". Hence, there is no treatment recommendation especially for postmenopausal women with increased lipid levels.

1.3 Principles of clinical research

Clinical research is performed to evaluate the safety and efficacy of medical interventions by means of clinical trials.[78] Clinical trials evaluate safety and efficacy in animals first. If beneficial, then safety and efficacy is evaluated in humans. Concerning efficacy evaluations in humans, clinical trials measure the average treatment effect. This means that in a trial with beneficial results not every participant in the intervention group has responded equally well but that, on average, the intervention was more efficacious than the control. Usually, those trials are performed prospectively, yield causal associations through randomization of patients and provide highest evidence for clinical decision-making, if performed correctly.[78,79] Randomization implies that the study is free of confounding variables, which otherwise skew the result because they are related to both the intervention and the outcome and are unequally distributed between intervention and control group. Correctly performed randomized controlled clinical trials further yield unbiased treatment effects, i.e. they are free of systematic errors and therefore yield the true effect estimate.[78]

It is not possible to answer all research questions in clinical trials due to infeasibility or ethical concerns. Infeasible research questions for example include rare diseases or diseases with a long lag time until they develop or progress (e.g. cancer, chronic diseases). Furthermore, trials are considered unethical if withholding lifesaving treatment or if they put patients at risk of

known adverse events in absence of equipoise with regard to the expected treatment effect (i.e. if adverse events are expected to outweigh the benefits).[80] In cases of studies needed other than for market approval of a new drug, observational research may fill the gap through the conduction of epidemiologic studies using previously collected medical data (e.g. from registries, electronic health records, administrative claims, multipurpose cohorts).[78]

1.3.1 Observational epidemiology at a glance

Observational epidemiology is the study of the distribution and determinants of disease frequency in a population.[81] There is descriptive research (describing the distribution of determinants and diseases, hypothesis generating studies) and analytical research (assessing the association between potential determinants and diseases, usually hypothesis testing studies).[82]

In observational epidemiology, analytical studies measure the real world effectiveness and safety of an exposure. Their results are usually generalizable to a larger patient population than the results of restricted populations in clinical trials. Applied study designs and statistical methods are manifold and are continuously expanded to tackle bias and unmeasured confounders. Bias and confounding in observational epidemiology are mainly due to the circumstances that the data was previously collected for other purposes (e.g. some data needed may not be available) and that the reason why patients use a medication may be related to the outcome as well.[82] What cannot be tackled through design and methods is data quality. Therefore, before data can be used for observational studies, it needs to be carefully cleaned and validated considering that the data quality is the foundation for any study that arises from the respective data source.[82] Medical data in Europe often stem from longitudinal patient record databases collected at the point of care (e.g. Clinical Practice Research Datalink [CPRD] in the UK, *SIDIAP* in Catalonia, Spain, *Intercontinental Marketing Service Disease Analyzer* [now part of *IQVIA*] in various European countries).[83]

1.3.2 Clinical Practice Research Datalink

The CPRD is a UK primary care database containing – as of July 2013 – medical information on around 11.3 million patients in 674 practices across the UK, out of whom 4.4 million patients were active at the time (i.e. alive, registered, and have not opted out as of July 2013) which corresponds to around 7% of the UK population.[84] Patients were representative of the UK

population concerning age, sex, and ethnicity when compared to the UK census in 2011, and representative of body mass index (BMI) when compared to the *Health Survey for England* (comparison performed up to 2010[85]).[84] However, CPRD practices are not representative of all practice in the UK with regards to geography and number of patients.[84]

The CPRD as it is known today has originated as a general practice information system in the 1980s. Taken over by a venture capital company named *Value Added Medical Products Ltd* (again taken over by Reuters in 1993), the company handed out computers to general practitioners (GPs) as incentives to participate and manage their patient files electronically as of 1987.[83] Since 1994, the CPRD belongs to the UK Department of Health.[86,87] The CPRD is unique in the way that the GP acts as a gate keeper within the UK National Health Service, can be consulted free of charge (98% of the UK population are registered with a GP), and receives feedback from secondary care.[84] Thereby, the GP keeps near complete medical patient records. Practices have only been allowed to participate in CPRD if they collected routine data with sufficient scrutiny according to a pre-defined standard (data quality checks throughout their participation included).[86] In participating practices, data is collected automatically as part of day-to-day medical care.[86] Patients' conditions (i.e. symptoms, diagnoses) are entered as so called Read codes.[84] All entries are made in standard software and are transferred via specially designed software as de-identified patient data to the Office for National Statistics which maintains and runs the database on behalf of the UK Department of Health.[86] Recorded data include demographics, prescriptions including dosage and quantity, symptoms, diagnoses, lifestyle measures (e.g. smoking status, BMI), results of laboratory tests, preventive care, immunization, death, specialist referrals, hospital admissions, and other feedback from secondary care (e.g. diagnoses, procedures, and admission and discharge dates for hospital visits).[84] Notably, not all entries are subject to a face-to-face consultation[84] and not all consultation are subject to an entry in the medical chart (e.g. if there is nothing to add in the patient record)[86]. The CPRD maintains a bibliography which counted over 2'000 publications in peer-reviewed journals as of December 2018.[88] This is to no surprise as the CPRD is one of the largest databases of longitudinal records from primary care worldwide[84] and its recorded diagnoses were repeatedly shown to be of high validity[89,90].

Aims and Objectives

2 Aims and Objectives

It is known that hand OA in women mainly develops after menopause. Hypotheses about the pathophysiologic mechanism between menopause and hand OA are estrogen depletion and systemic inflammation through unfavorable changes in circulating lipids and fat mass deposition.

Small observational studies investigating the effect of HRT (principal treatment of postmenopausal estrogen depletion) and hand OA yielded contradictory results. Prior evidence assessing the relationship between statins (principal lipid lowering treatment) and hand OA in peri-to-postmenopausal women did not exist.

To help find drugs potentially delaying hand OA onset by describing and assessing drugs treating symptoms evolving in menopausal transition in association with hand OA, we performed the following epidemiologic studies:

1) A descriptive study estimating IRs of HRT use and hand OA over time and by age group.
2) A nested case-control analysis assessing the association between HRT use and hand OA overall, by timing of HRT use (current or past use), and in women with recorded menopause only. In a secondary analysis, we assessed the association between menopause and hand OA. Furthermore, in women with recorded menopause only, we assessed the timing of HRT initiation relative to menopause in current users and of HRT cessation relative to hand OA diagnoses in past users, compared to non-users.
3) A cohort study assessing the association between incident statin use and new onset of hand OA in peri-to-postmenopausal women overall, by age group, absent or present dyslipidemia diagnosis, and by duration of follow-up. In a secondary analysis, we assessed the association between incident statin use and new onset of generalized OA. Through the use of psoriasis and tinnitus as negative control outcomes, we aimed to qualitatively assess our results for confounding by differential menopause onset and healthcare seeking behavior.

A potential negative association between the respective drug initiation and hand OA onset may result in a decreased burden of this incurable disease.

Methods, Results, and Discussions

3 Methods, Results and Discussions

3.1 Incidence rates of hormone replacement therapy use and of hand osteoarthritis: A descriptive study

The subsequent work is based on data of the following publications:

Burkard T, Moser M, Rauch M, Jick SS, Meier CR. **Utilization pattern of hormone therapy in UK general practice between 1996 and 2015: A descriptive study** *Menopause.* 2019;26(7):000-000 (ahead of print)

Please see Appendix 1.

Burkard T, Rauch M, Spoendlin J, Prieto-Alhambra D, Jick SS, Meier CR. **Risk of hand osteoarthritis in new users of hormone therapy: A nested case-control analysis** *Submitted to Maturitas*

Please see Appendix 2.

The studies were approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research with protocol 18_034R and 18_089R, respectively.

3.1.1 Methods

Study design and data source

We conducted a population-based descriptive study using data derived from the UK-based CPRD. A study is called population-based if it is performed among a major or representative sample of the underlying population (i.e. the study is large in size or has a non-restrictive study population).[82] Descriptive studies usually describe how personal characteristics (e.g. age, sex, ethnicity, place of residence, socioeconomic status) relate to an underlying disease or trends in drug utilization.[82] A further tool of descriptive studies is the description of temporal trends, which may generate new or underpin existing hypotheses.[82]

Study population

We identified all women aged 40-69 years (based on their year of birth) between January 1996 and December 2015 (study period) in the CPRD. From this study population, we selected two cohorts (a cohort comprises patients who have particular characteristics in common).

1) For description of incidence rates of HRT use, we identified women who had no HRT prescriptions before age 40 (based on their year of birth), had ≥3 years of history in the database before their first HRT prescription, and who had ≥1 GP contact prior to their first HRT prescription.
2) For description of incidence rates of hand OA, we identified women who had no hand OA diagnosis before age 40 (based on their year of birth), had ≥3 years of history in the database before their first hand OA diagnosis, and who had ≥1 GP contact prior to their first hand OA diagnosis.

Outcomes

HRT was defined as a recorded prescription for any unopposed or opposed HRT (includes separate estrogen and progestogen prescriptions prescribed within the same calendar year), or tibolone product, regardless of route of administration.

Hand OA was defined as a first hand OA diagnosis (primary or secondary) or a diagnosis of hand pain if followed by an incident diagnosis of hand OA, OA, or generalized OA within 365 days.

Data analysis

We divided the study period into twenty 1-year blocks and estimated annual IRs of HRT use and hand OA. Throughout the study period, we estimated IRs of HRT use and of hand OA stratified by age groups (40-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, 65-69 years).

In a post-hoc analysis to account for the strong time trend in HRT initiation, we divided the study period by two (1996-2002 and 2003-2015). In each study period, we estimated IRs of HRT use and of hand OA stratified by age groups (40-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, 65-69 years).

We calculated IRs of 1) new HRT use and of 2) hand OA by dividing the number of 1) new HRT prescriptions and 2) hand OA diagnoses by the respective accumulated pys at risk.

3.1.2 Results

From 1996 to 2015, we identified 229,104 new HRT users and 20,274 women with an incident diagnosis of hand OA among the study population. Figure 3 depicts annual IRs of HRT use and hand OA over time. Corresponding numeric values are displayed in Appendix 3.

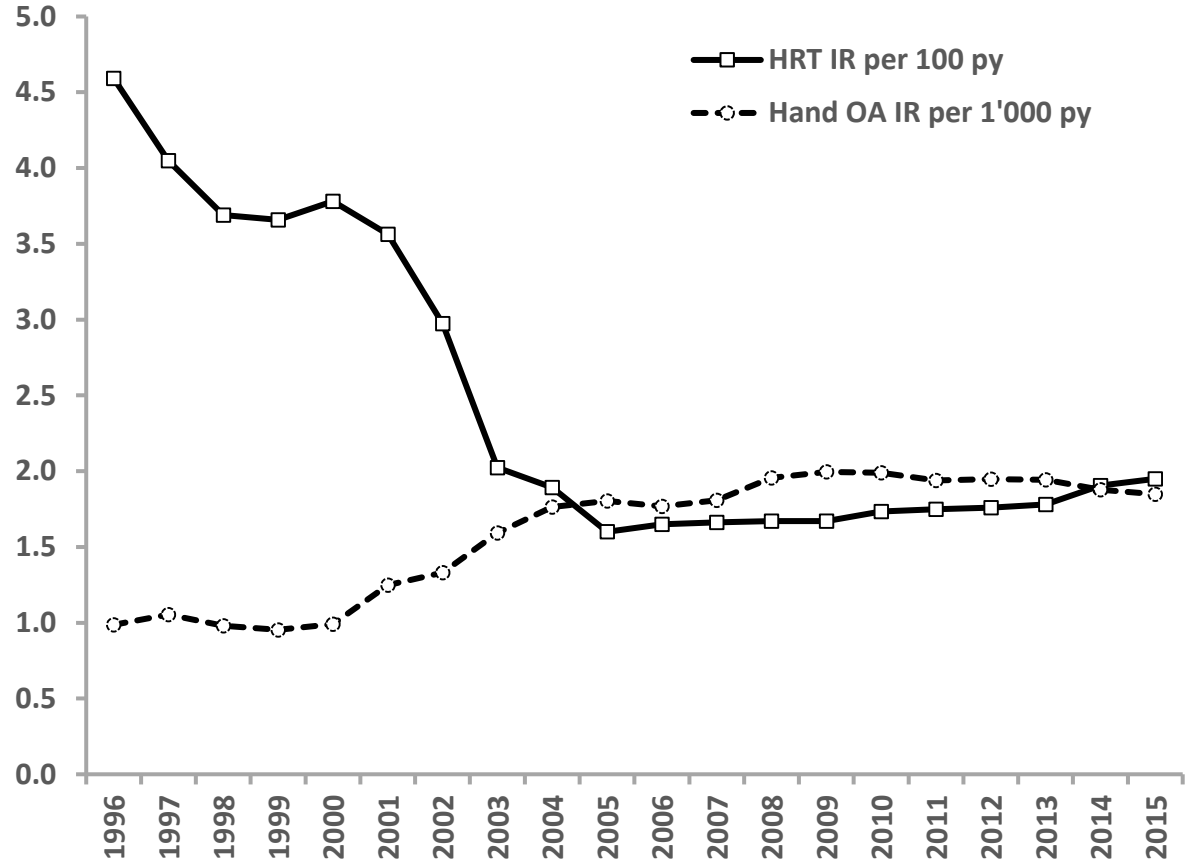

Fig3. Annual incidence rates of hormone replacement therapy use and of hand osteoarthritis in women aged 45-69 from 1996 to 2015
HRT: hormone replacement therapy, IR: incidence rate, py: person-years, OA: osteoarthritis

IRs of HRT use dropped from a maximum of 4.6/100 py in 1996 to a plateau of 3.6-3.8/100 py between 1998 and 2001, then halved to 2.0/100 py in 2003, followed by a slight decrease to a minimum of 1.6/100 py in 2005, and slowly increased up until 1.9/100 py in 2015.

Hand OA IRs plateaued from 1996 until 2000 at around 1.0/1'000 py followed by an increase to a pleateau at around 1.8/1'000 py between 2004 and 2007. Thereafter, hand OA IRs

increased to another plateau at around 2.0/1'000 py until 2013 before slightly decreasing again.

Figure 4 depicts IRs of HRT use and hand OA stratified by age group. Corresponding numeric values are displayed in Appendix 4.

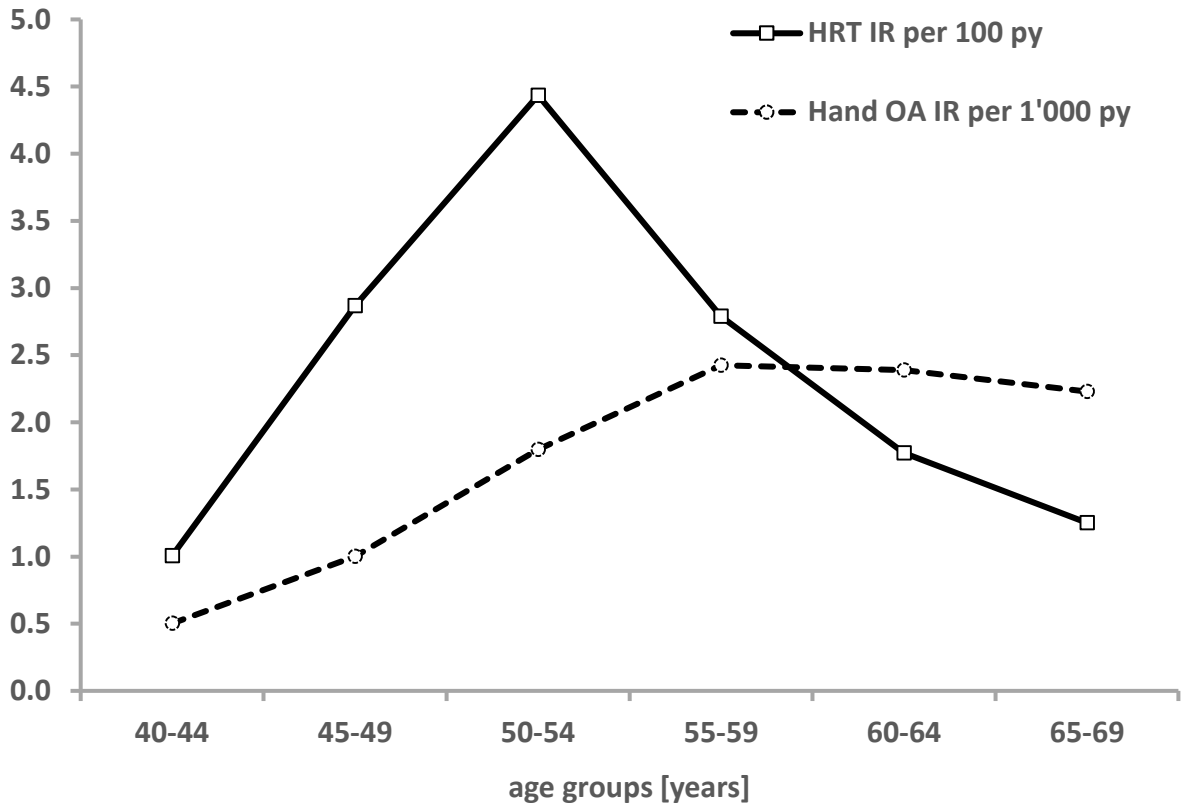

Fig4. Incidence rates of hormone replacement therapy use and hand osteoarthritis in women stratified by age group
HRT: hormone replacement therapy, IR: incidence rate, py: person-years, OA: osteoarthritis

IRs of HRT use increased from 1.0/100 py in women aged 40-44 to 4.4/100 py in women aged 50-54 before decreasing again to 1.3/100 py in women aged 65-69.

Hand OA IRs increased with increasing age from age 40-44 at 0.5/1'000 py to 2.4/1'000 py in 55-59 year old women, and plateaued thereafter.

Figure 5 depicts IRs of HRT use stratified by age group and study period. Corresponding numeric values are displayed in Appendix 5.

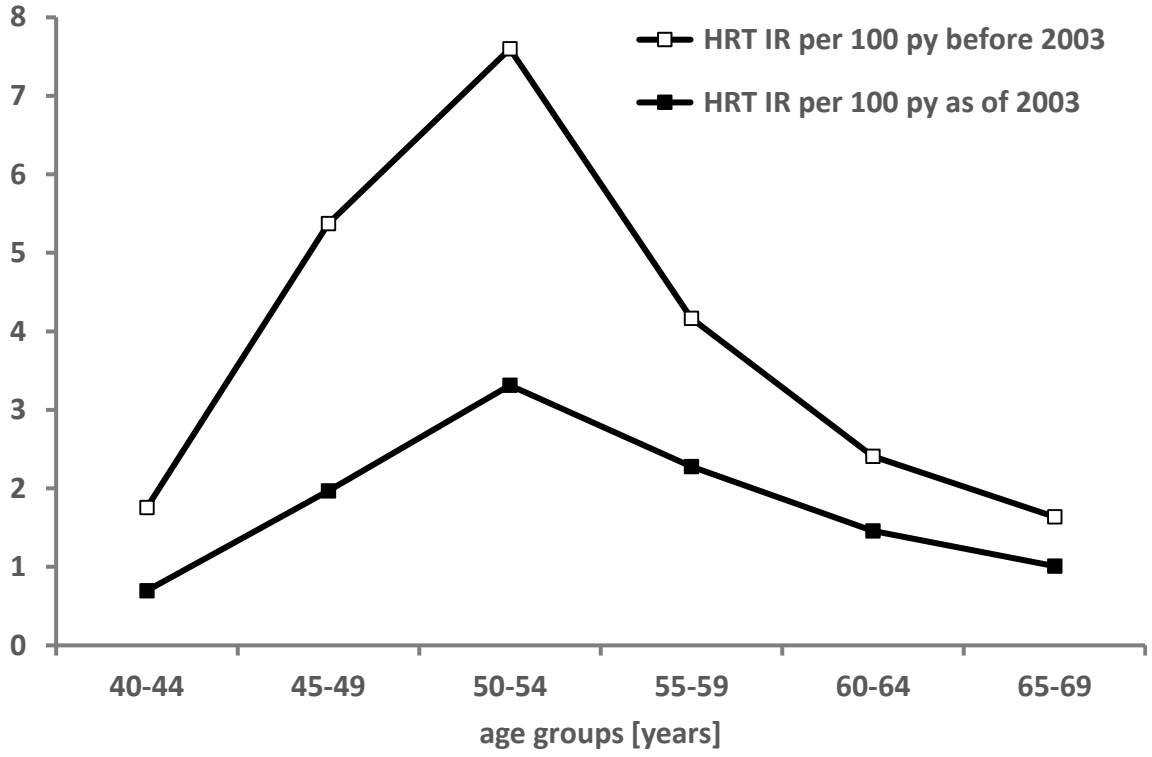

Fig5. Incidence rates of hormone replacement therapy use in women stratified by age group and study period
HRT: hormone replacement therapy, IR: incidence rate, py: person-years

IRs of HRT use in age groups before and as of 2003 followed a similar pattern. IRs of HRT use before 2003 yielded a stronger increase in women aged 45-49 years and a higher peak (7.6/100 py) in women aged 50-54 years, compared to a peak of 3.3/100 py in women of the same age group who initiated HRT as of 2003. After the peaks, IRs of HRT use before 2003 and as of 2003 declined and converged to 1.0/100 py and 1.6/100 py, respectively, in women aged 65-69.

Figure 6 depicts IRs of hand OA stratified by age group and study period. Corresponding numeric values are displayed in Appendix 6.

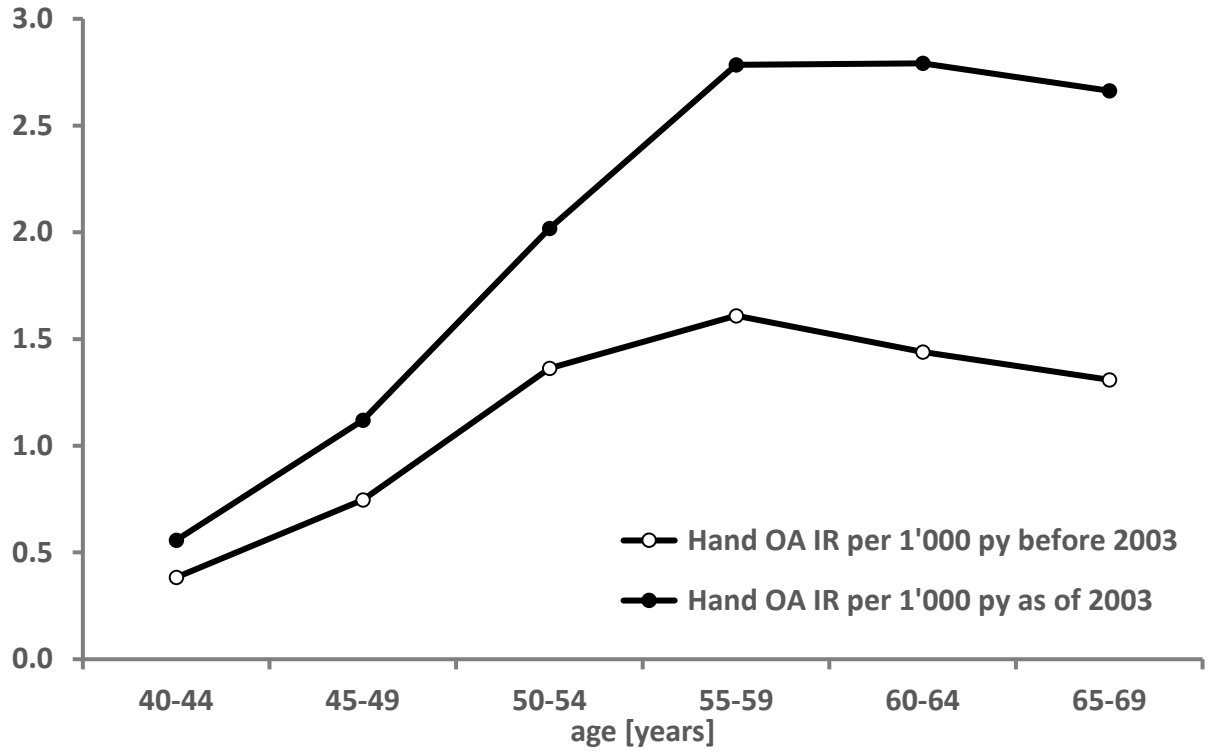

Fig6. Incidence rates of hand osteoarthritis in women stratified by age group and study period
OA: osteoarthritis, IR: incidence rate, py: person-years

IRs of hand OA in age groups before and as of 2003 increased similarly until 1.4/1'000 py and 2.0/1'000 py, respectively, in women aged 50-54, when IRs of hand OA in age groups started to diverge. As of 2003, IRs of hand OA increased further until a peak in women aged 55-59 and a subsequent plateau at around 2.7/1'000 py, while, before 2003, IRs of hand OA increased only slightly until a peak in women aged 55-59 at 1.6/1'000 py and decreased slowly subsequently.

3.1.3 Discussion

In this descriptive study in the UK-based CPRD between 1996 and 2015, we described IRs of HRT use and of hand OA in women between 40 and 69 years of age. We observed that IRs of HRT use and of hand OA behaved inversely over time and uniformly in 5-year age groups of 40 to 54 years but not in older age groups.

IRs of HRT use dropped by around 20% from 1996 to a plateau between 1998 and 2001 as a likely consequence of increased breast cancer risks associated with HRT use reported continuously since the 1980s.[91] It might have declined more rapidly if not for the common belief of a protective effect of HRT on CVD at the time.[92–94] However, in 2002, an associated

increased risk of CVD was found by the well-known randomized controlled trial Women's Health Initiative (WHI).[58] As a likely consequence, IRs of HRT use almost halved until 2003. A study assessing reasons for HRT initiation pre-and post-WHI in the United States reported that provider advice, youth-preservation, and prevention of osteoporosis, CVD, and memory loss had decreased as reasons for HRT initiation post-WHI compared to pre-WHI.[95] Furthermore, irrespective of duration of vasomotor symptoms, only around one third of women initiated HRT post-WHI compared to pre-WHI.[95] The authors concluded that women with a low risk profile of CVD in their 50s may have forgone HRT for vasomotor symptom relief due to improper interpretation of associated risks post-WHI.[95] In 2005, the turning point of IRs of HRT use was reached when IRs of HRT use started to slowly increase up again until 2015. In 2015, the HRT initiation level of 2003 was reached reflecting a potential ongoing underutilization in women suffering from postmenopausal symptoms with a positive risk-benefit profile when assuming similar reactions to WHI of UK women as of US women.

Observed IRs of hand OA in women over time followed the same pattern as age standardized IRs of clinical hand OA (including hand pain) reported by Yu et al. in a population-based study using the same data source, but were around 50% lower.[12] Yu et al. reported IRs in women to plateau at around 1.5-2/1'000 py from 1992 until 1996 before increasing to 5.25/1'000 py in 2013.[12] Increasing IRs of hand OA over time may be due to better understanding of the disease and therefore better diagnosing, and also potentially raised awareness and therefore more thorough coding. Yu et al. reported age-standardized IRs of hand OA in men, which were lower than those in women but followed the same pattern as those in women over time.[12]

IRs of HRT use in age groups almost followed the Gaussian curve of natural menopause onset between age 40 to age 60 irrespective of the observation period.[37] As of age 40, IRs of HRT use increased until a peak in women aged 50-54 years, however, did not decrease quite as strongly but showed a tail in age groups ≥60 years. With women and prescribers anxious about HRT use post-WHI,[95] post-WHI HRT initiators were likely women with severe postmenopausal symptoms as HRT initiation rates were much lower, especially among women aged 45 to 54 years, when compared to HRT initiation rates pre-WHI. However, in women aged ≥60 years, the difference in HRT initiation between pre- and post-WHI was small. This was likely due to women initiating HRT to treat genitourinary symptoms (mainly treated with vaginal HRT with

no or low systemic uptake) in these age groups as these symptoms present rather late during postmenopausal age and were reported to increase in severity with age.[96]

Observed IRs of hand OA in age groups also followed a similar course compared to those reported by Yu et al. (based on data from year 2000) but were also generally lower by around 40%, and by around 30% when assessing IRs of hand OA before 2003.[12] Yu et al. reported IRs of hand OA to peak at around 4/1'000 py in women aged 55 to 60 years old and to slowly decrease thereafter to around 2/1'000 py at age 85 with men not following this pattern.[12]

Reasons for lower IRs of hand OA in our study compared to Yu et al. may be due to our requirement that a hand pain diagnosis had to be followed by a diagnosis of hand OA, OA, or generalized OA while Yu et al. accepted a hand pain diagnosis above the age of 45 as clinical hand OA. However, Yu et al. censored follow-up time in patients with differential diagnoses of hand OA potentially leading to lower IRs (when we took differential indications into account, IRs of hand OA lowered by around 5%, data not shown). Furthermore, Yu et al. used fewer Read codes for hand OA which should have also resulted in lower IRs. Both studies applied a 3-year run-in period while they used additional inclusion criteria concerning CPRD practices. Differences in magnitude of hand OA IRs remain unexplained but observed patterns of hand OA IRs were highly similar with those reported by Yu et al[12].

A major strength of this study is its very large patient population of >2 million women yielding informative results. Additionally, as CPRD prescriptions are issued electronically by the GP, we likely captured near complete patient prescription records, especially since HRT suggestions from specialists such as gynecologists and endocrinologists, who may treat women at high risk of adverse events, are issued by the GP for reasons of reimbursement.

3.2 Risk of hand osteoarthritis in new users of hormone replacement therapy: A nested case-control analysis

The subsequent work is based on the following manuscript:

Burkard T, Rauch M, Spoendlin J, Prieto-Alhambra D, Jick SS, Meier CR. **Risk of hand osteoarthritis in new users of hormone therapy: A nested case-control analysis** *Submitted to Maturitas*

Please see Appendix 2.

The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research with protocol 18_089R.

3.2.1 Methods

Study design and Data source

We conducted a nested case-control study using data derived from the UK-based CPRD. We further used CPRD-linked patient level data on socio-economic status (index of multiple deprivation, IMD), which is available for patients living in England only.[97,98]

A nested case-control study is a case-control study nested within a well-defined cohort,[99] meaning that controls are randomly sampled from the same cohort population in which cases are identified. In case-control studies, odds ratios (ORs) are estimated by dividing exposure odds of cases by exposure odds of controls. ORs transfer the information whether the exposure is a risk factor (OR >1) or a beneficial factor (OR <1) of the outcome.[79] An OR is called "crude" if there is no adjustment for confounders in the statistical model (i.e. a simple division of exposure odds, also called simple logistic regression). If confounders are put into the statistical model (i.e. a multivariable logistic regression model), the OR is called "adjusted" for confounders and implies that the result is free of potential confounding by these variables, given that the variables were measured correctly.

Study population

We included all women on July 1st (cohort entry) of the year in which they turned 45 years old (based on their year of birth) between January 1998 and December 2017 in an inception

cohort. In contrast to a regular cohort, an inception cohort only comprises patients who have an incident common characteristic, here, age 45.

We excluded all women with ≤1 year of active history and/or <1 GP visit on the database prior to cohort entry. We further excluded women with a history of hand OA and with diseases potentially linked to secondary OA or differential diagnoses of hand OA prior to cohort entry, namely hemarthrosis of the hand, malformation or misalignments of the fingers, hypermobility syndrome, hyperparathyroidism, acromegaly, previous finger injury (e.g. fracture, dislocation, tear of ligament), Stickler syndrome, Paget's disease, disorder of iron metabolism (hemochromatosis), inflammatory polyarthropathies, and Wilson disease.[14,100,101] Women were not eligible if they had a recorded Read code for any cancer (except non-melanoma skin cancer), alcoholism, alcohol/ other substance abuse, or human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) at any time prior to cohort entry. Furthermore, women were excluded if they had a prescription of systemic HRT prior to cohort entry.

Follow-up and Case definition

We followed all women from cohort entry until they developed incident hand OA defined as 1) a first-time Read code for hand OA or 2) a record of hand pain followed by an incident Read code of hand OA, OA, or generalized OA within 365 days thereafter (these women are further referred to as "cases" and the date of their first hand OA or hand pain diagnosis as the "index date"). Follow-up was censored at the first of the following: recorded exclusion criterion described above (except for first-time systemic HRT use), disenrollment from the CPRD, age 65, or the end of the study period (December 2017). Read codes in CPRD do not differentiate between primary and secondary hand OA diagnoses. However, as we were interested in primary hand OA cases, we excluded women with causes of secondary hand OA and censored women when a diagnosis for a potential cause of secondary hand OA was recorded.

Definition of Controls

Each hand OA case was matched to four controls from the inception cohort who did not have a record of hand OA up to 180 days prior to the case index date (risk-set sampling[102] with a lag period to account for gradual disease onset) on age, calendar date (index date of the case), GP practice, and years of history in the CPRD before the index date.

Risk-set sampling (also called incidence density sampling) implies that patients at risk of becoming a case are selected as controls from the study population each time a case is diagnosed.[82,99] The patients who are "at risk" when a case is diagnosed are also called the "risk-set".[82,99] Risk-set sampling ensures that controls are selected in proportion to the time they contribute person-time at risk (i.e. a patient who is "at risk" longer is more likely to serve as a control or to serve as a control several times).[99] Furthermore, when assessing incident cases, ORs are equal to rate ratios of cohort studies (explanation of rate ratios and cohort studies on page 41). This is because resulting risk estimates will be almost identical to estimates that would have been obtained in the underlying cohort, but with wider CIs.[102] Moreover, after risk-set sampling, resulting risk estimates are not biased by differential censoring.[82,99]

Exposure

We defined new HRT use as a first ever recorded prescription for any systemic unopposed or opposed HRT (includes separate estrogen and progestogen prescriptions prescribed within close proximity). Possible routes of administration were oral, transdermal (i.e. patch), topical (i.e. gel), nasal, implanted, or injected. We did not include vaginal HRT administrations due to their relatively low, variable systemic bioavailability.

A woman was considered exposed from the day after the first HRT prescription, and was considered "currently exposed" for as long as each prescription was followed by a subsequent prescription within a grace period of 180 days after the alleged end of supply (Figure 7).

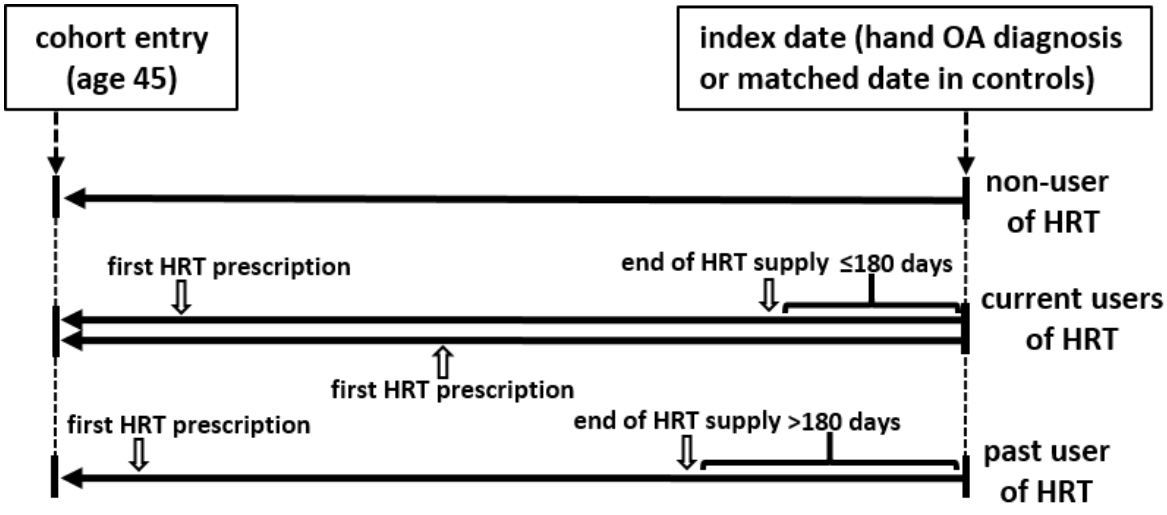

Fig7. Hormone replacement therapy exposure definition in the case-control analysis
OA: osteoarthritis, HRT: hormone replacement therapy

Supply length was determined based on the number of prescribed products and dose instructions. In case of missing or improbable information on supply length, we used previously assessed default values of product quantities and dosing. A person was classified as having past exposure from day 181 after a current prescription supply ended (Figure 7). Past users were censored whenever a new systemic HRT prescription was recorded (i.e. past users could not become current users again).

Covariates

We assessed the following potential confounders of the association between HRT initiation and hand OA (selected *a priori* based on clinical knowledge) recorded at any time before the index date (if not specified otherwise): BMI ≥30 kg/m^2 (Read code or measure for BMI),[65,66,68,75,103,104] current smoking,[66,68,69,104] heavy alcohol consumption >14 units/week,[68] osteoporosis (Read code or prescription for bone-modifying drug),[65,75,104,105] diabetes (Read code or antidiabetic drug), thiazide prescriptions,[66] dyslipidemia (Read code or laboratory value), a vaccination record (proxy for healthcare seeking behavior), and >5 GP contacts[103] within 1 year prior to cohort entry (proxy for healthcare seeking behavior; we assessed GP contacts prior to cohort entry because assessing GP contacts prior to the index date may lie on the causal pathway between HRT initiation and being diagnosed with hand OA). With dichotomization of lifestyle covariates, we assumed that women with a missing record of BMI (9.0%), smoking status (2.8%), or alcohol consumption (8.3%) were non-obese, non-smokers, or non-heavy drinkers. We further assessed any time vaginal HRT use and socio-economic status in quintiles of IMD (where quintile 1 represents least deprived and quintile 5 most deprived). Menopause (natural or surgically induced) was assessed between cohort entry and the index date.

Statistical analysis

We conducted multivariable conditional logistic regression analyses to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) of the association between new HRT use compared to non-use and hand OA overall, and stratified by timing of HRT use (currently exposed, past exposed).

We performed the following sensitivity analyses (analyses to qualitatively analyze the level of certainty of results of the main analysis by being stricter with inclusion/exclusion criteria, the outcome or other features of the study):

1) We further adjusted the analysis for vaginal HRT use as we neglected vaginal HRT use due to its rather low and variable systemic uptake.

2) We further adjusted the analysis for socio-economic status in women with available information on IMD (ordinal variable) as socio-economic status is a potential confounder of the association between HRT use and hand OA.

3) As hand OA is a diagnosis mainly made in primary care, we could not validate diagnoses using secondary care data. Nonetheless, we restricted cases to women with a diagnosis of incident hand OA that was preceded or followed by a specialist referral/ discharge (rheumatologist/ orthopedist/ radiologist), or diagnostic work up (MRI, X ray, ultrasonography) within 90 days before or after the diagnosis.

4) Furthermore, to account for the slowly developing character of hand OA potentially leading to a delayed diagnosis, we re-analyzed the data with the index date shifted to 180 days before the hand OA diagnosis date or matched date in controls.

To assess confounding by whether or not a woman had menopause recorded in the database, we calculated crude and adjusted ORs of hand OA in women with recorded menopause compared to women who had no menopause record (menopause records between cohort entry and the index date only, women with a menopause record before cohort entry were excluded in this analysis). Because we observed an association between the presence of recorded menopause and a diagnosis for hand OA, we restricted the remainder of analyses to women with recorded menopause. In these women, we estimated ORs of the association between hand OA and new HRT use, compared to non-use overall and stratified by timing of HRT use (currently exposed, past exposed). We further estimated ORs stratified by timing of HRT initiation relative to recorded menopause in current users compared to non-users (>3 months before menopause [range: 140-2811 days], ≤3 months before/after menopause, 3-36 months after menopause, and >36 months after menopause [range: 1126 4474 days]). Furthermore, we estimated ORs stratified by timing of HRT cessation before the index date among past users, compared to non-users (≤18 months before the index date, >18-54 months

before the index date, and >54 months before the index date). Moreover, to describe the temporal trend of hand OA onset after menopause, we described the proportion of hand OA cases in women with recorded menopause after cohort entry in 1-year intervals after recorded menopause (Figure 8). Proportions were estimated by dividing the number of hand OA cases in each interval by the number of total hand OA cases at any time between cohort entry and index date. We performed all analyses using SAS statistical software version 9.4 (NC, USA).

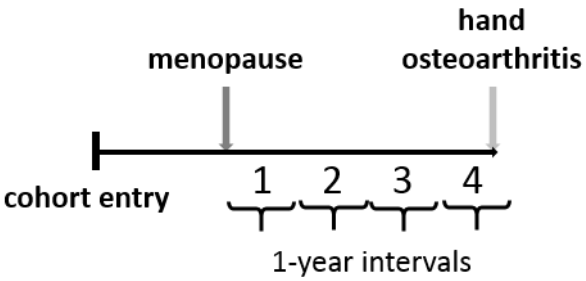

Fig8. Scheme of determining 1-year intervals after recorded menopause

In a post-hoc analysis, we assessed whether potential residual confounding was strong enough to explain observed results in the stratum of women who initiated HRT ≤3 months before/after recorded menopause using the array approach as described by Schneeweiss[106]. The array approach was performed using a tool made available by the Division of Pharmacoepidemiology and Pharmacogenomics from Harvard University, Massachusetts, USA.[107]

3.2.2 Results

We identified 623,671 women who turned 45 years old during the study period. After application of exclusion criteria, 438,674 women entered the inception cohort (Figure 9).

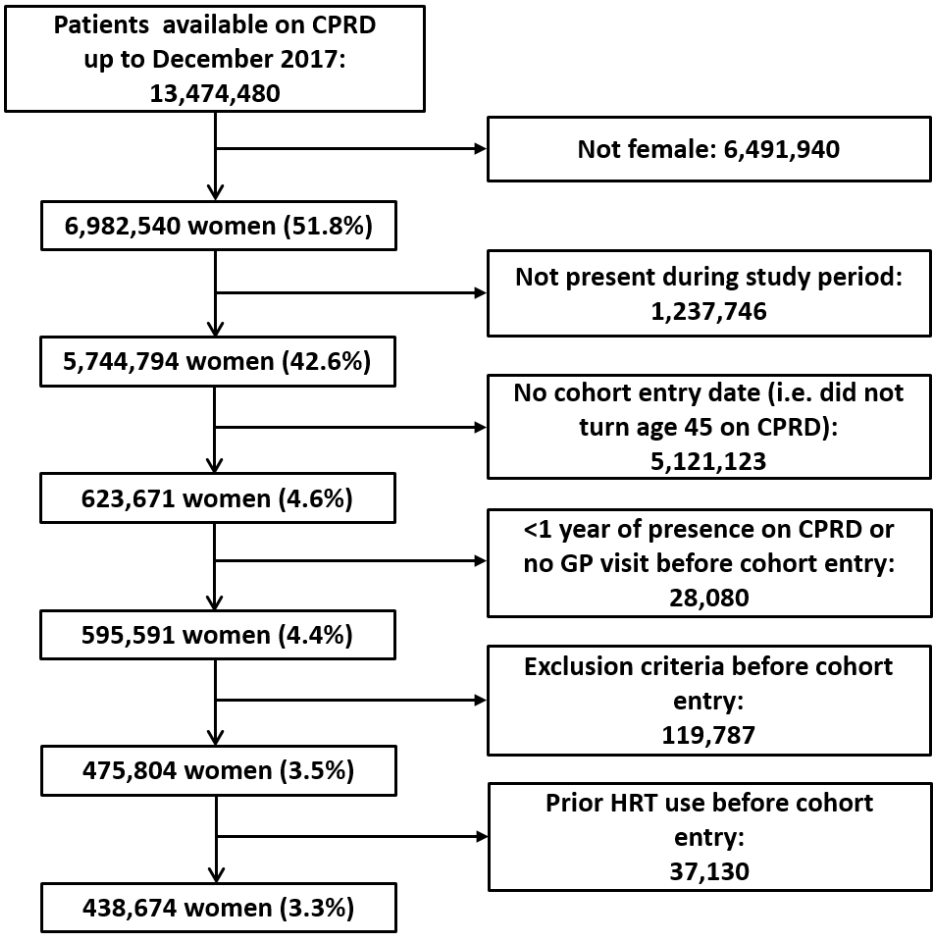

Fig9. Flow chart of the study composition
CPRD: Clinical Practice Research Datalink, GP: general practitioner, HRT: hormone replacement therapy

Among the cohort, we identified 3440 hand OA cases and 13,760 matched controls. Characteristics of these women are displayed in Table 1. The mean age of cases and controls at the index date was 50.9 years (standard deviation: 4.1 years). Cases had more recorded diagnoses of osteoporosis, diabetes, dyslipidemia, and obesity, and also saw their GP more often in the year prior to cohort entry, than controls.

Tab1. Patient characteristics of cases and matched controls before the index date

Variables used for matching or covariate adjusting in logistic regression	Cases (n=3440)	Controls (n=13,760)
Mean age at index date (SD)	50.9 (4.1)	50.9 (4.1)
Mean number of years of history in the database (SD)	15.9 (5.6)	15.9 (5.6)
>5 GP contacts ≤1 year prior to cohort entry*	2573 (74.8%)	8474 (61.6%)
Osteoporosis (%)	63 (1.8%)	210 (1.5%)
Smokers (%)	592 (17.2%)	2435 (17.7%)
Heavy alcohol drinker (>14 units/week) [%]	100 (2.9%)	415 (3.0%)
Diabetes diagnosis (%)	148 (4.3%)	502 (3.7%)
Thiazide prescriptions (%)	454 (13.2%)	1405 (10.2%)

Dyslipidemia diagnosis or according laboratory value (%)	1174 (34.1%)	4018 (29.2%)
Obesity diagnosis or BMI≥30 kg/m^2 (%)	907 (26.4%)	3364 (24.5%)
Vaccine use (%)	1619 (47.1%)	6086 (44.2%)
Additional variables used in sensitivity/subgroup analyses		
Vaginal hormone replacement therapy use	218 (6.4%)	670 (4.9%)
IMD quintile 1 (least deprived)	632 (18.4%)	2424 (17.6%)
IMD quintile 2	498 (14.5%)	2024 (14.7%)
IMD quintile 3	393 (11.4%)	1567 (11.4%)
IMD quintile 4	321 (9.3%)	1348 (9.8%)
IMD quintile 5 (most deprived)	229 (6.7%)	914 (6.6%)
IMD unknown	1367 (39.7%)	5483 (39.9%)
Recorded menopause after cohort entry	860 (25.0%)	2610 (19.0%)

SD: standard deviation, GP: general practitioner, BMI: body mass index, IMD: index of multiple deprivation
*number of GP contacts prior to the index date would lie on the causal pathway

The adjusted OR of hand OA in current HRT users compared to non-users was 1.32 (95% CI 1.17-1.48) [Table 2].

Tab2. Odds ratios of hand osteoarthritis in association with hormone replacement therapy overall and stratified by timing of hormone replacement therapy use at the index date

Overall	**Cases: 3440 (%)**	**Controls: 13,760 (%)**	**OR crude (95% CI)**	**OR adjusted* (95% CI)**
No HRT use	2982 (86.7)	12,415 (90.2)	1.00 ref	1.00 ref
Overall HRT use	458 (13.3)	1345 (9.8)	1.45 (1.29-1.63)	1.32 (1.17-1.48)
Overall HRT use additionally adjusted for vaginal HRT use				1.31 (1.16-1.47)
Current HRT use	189 (5.5)	627 (4.6)	1.27 (1.07-1.50)	1.11 (0.93-1.31)
Past HRT use	269 (7.8)	718 (5.2)	1.62 (1.39-1.89)	1.52 (1.31-1.78)
Women with information on IMD	**Cases: 2073 (%)**	**Controls: 8277 (%)**	**OR crude (95% CI)**	**OR adjusted* (95% CI)**
No HRT use	1797 (86.7)	7480 (90.4)	1.00 ref	1.00 ref
Overall HRT use additionally adjusted for IMD in quintiles	276 (13.3)	797 (9.6)	1.47 (1.27-1.72)	1.34 (1.15-1.57)
Index date shift to 180 days before the index date†	**Cases: 3308 (%)**	**Controls: 13,154 (%)**	**OR crude (95% CI)**	**OR adjusted* (95% CI)**
No HRT use	2850 (86.2)	11,813 (89.8)	1.00 ref	1.00 ref
Overall HRT use	458 (13.9)	1341 (10.2)	1.31 (1.19-1.45)	1.23 (1.11-1.36)
Cases with a secondary care entry‡	**Cases: 660 (%)**	**Controls: 2640 (%)**	**OR crude (95% CI)**	**OR adjusted* (95% CI)**
No HRT use	572 (86.7)	2403 (91.0)	1.00 ref	1.00 ref
Overall HRT use	88 (13.3)	237 (9.0)	1.62 (1.23-2.14)	1.43 (1.08-1.89)

OR: odds ratio, CI: confidence interval, HRT: hormone replacement therapy, IMD: index of multiple deprivation
* adjusted for osteoporosis, smoking, alcohol consumption, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use prior to index date and for number of GP contacts prior to cohort entry
† cases with ≤180 days of follow-up and their matched controls as well as any control with ≤180 days of follow-up were excluded
‡ hand osteoarthritis preceded or followed by a specialist referral/discharge (rheumatologist, orthopedist, or radiologist) or diagnostic work up (MRI, X ray, ultrasonography) within 90 days before or after the diagnosis. Other hand osteoarthritis cases and their matched controls were excluded

A record of menopause (irrespective of HRT use) was associated with an increased adjusted OR of hand OA of 1.42 (95% CI 1.29-1.57) when compared to women without recorded menopause (Figure 10).

Women with or without recorded menopause after cohort entry and before the index date	**Cases: 3085 (%)**	**Controls: 12,681 (%)**	**OR adjusted* (95% CI)**
No recorded menopause	2225 (72.1)	10,071 (79.4)	1.00 ref
Recorded menopause	860 (27.9)	2610 (20.6)	1.42 (1.29-1.57)
No HRT use	604 (19.6)	1821 (14.4)	1.00 ref
Overall HRT use	256 (8.3)	789 (6.2)	0.98 (0.85-1.14)
Current HRT use	106 (3.4)	378 (3.0)	0.85 (0.69-1.04)
… HRT start >3 months before menopause	8 (0.3)	21 (0.2)	1.04 (0.52-2.09)
… HRT start ≤3 months before/after menopause	55 (1.8)	238 (1.9)	0.72 (0.55-0.96)
… HRT start 3-36 months after menopause	33 (1.1)	98 (0.8)	0.97 (0.68-1.37)
… HRT start >36 months after menopause	10 (0.3)	21 (0.2)	1.30 (0.69-2.43)
Past HRT use	150 (4.9)	411 (3.2)	1.10 (0.91-1.31)
… HRT stop ≤18 months before the ID	29 (0.6)	64 (0.3)	1.25 (0.86-1.81)
… HRT stop >18-54 months before the ID	65 (2.4)	170 (1.6)	1.11 (0.86-1.43)
… HRT stop >54 months before the ID	56 (1.8)	177 (1.4)	1.01 (0.76-1.33)

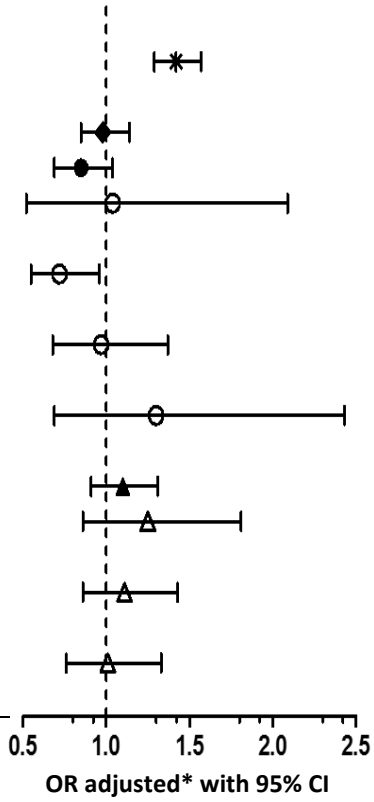

Fig10. Odds ratios of hand osteoarthritis in association with recorded menopause after cohort entry, and, in patients with recorded menopause after cohort entry, odds ratios of hand osteoarthritis in association with hormone replacement therapy and stratified by timing of hormone replacement therapy use (current/ past use) and by timing of hormone replacement therapy initiation relative to recorded menopause (in current users) and of hormone replacement therapy cessation before the index date (in past users)

HRT: hormone replacement therapy, ID: index date, OR: odds ratio, CI: confidence interval

* adjusted for osteoporosis, smoking, alcohol consumption, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use prior to index date, and adjusted for number of GP contacts prior to cohort entry.

In women with recorded menopause, there was no association between HRT use and risk of hand OA: adjusted OR 0.98 (95% CI 0.85-1.14) when compared to non-use. Current HRT users (versus non-users) had a statistically non-significantly decreased adjusted OR of hand OA of 0.72 (95% CI 0.49-1.05), when HRT was initiated within 3 months before/after menopause with ORs increasing with later HRT initiation. Women with past HRT use had a statistically non-

significantly adjusted OR of hand OA of 1.25 (95% CI 0.86-1.81) if HRT was stopped ≤18 months before the index date, which decreased towards the null with increasing duration between HRT cessation and the index date (Figure 10).

The proportion of women with hand OA diagnoses decreased with increasing number of 1-year intervals after recorded menopause. A maximum proportion of 18.4% of women had hand OA recorded (158 of 860 cases) within 1 year after recorded menopause. Cumulatively of all women who developed hand OA after menopause, 54.9% and 79.9% of women did so within 4 years and 7 years, respectively (Figure 11).

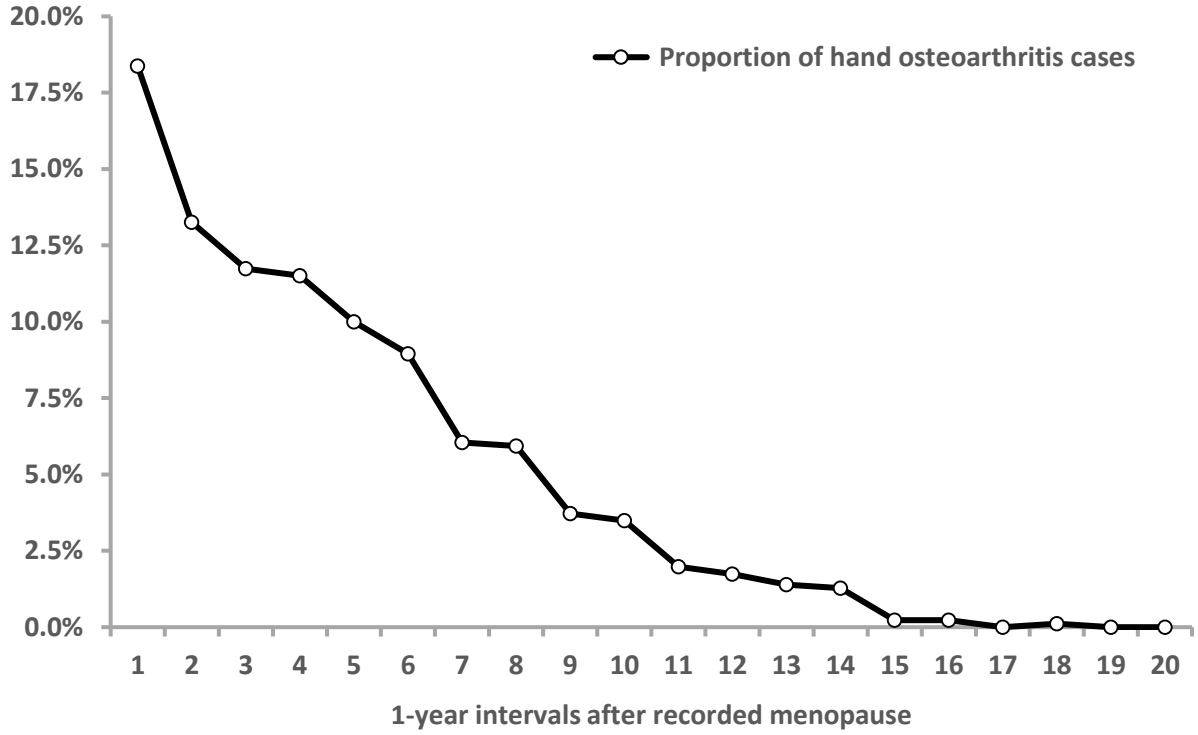

Fig11. Proportion of newly diagnosed hand osteoarthritis cases in 1-year intervals after recorded menopause

In all analyses, adjusted ORs of hand OA were lower in current and higher in past HRT users than when HRT was assessed overall (Table 2, Figure 10). When we further adjusted the overall analysis for vaginal HRT use and socioeconomic status (IMD available in 60.2% of women) in two sensitivity analyses, results remained unchanged (Table 2). In two further sensitivity analyses related to outcome validity, results remained largely unchanged as well (Table 2).

In a post-hoc analysis, we assessed the extent of residual confounding needed to potentially explain the decreased adjusted OR of hand OA of 0.72 in HRT initiators ≤3 months before/after

recorded menopause who were still HRT users at the index date, compared to non-initiators. To increase the observed adjusted OR to 1.0, a potential unmeasured confounder would need to have, for example, a prevalence of 15% and 0% in non-users and HRT users, respectively, and to achieve a relative risk of hand OA of 3.0 (the lower the prevalence in non-users or the higher the prevalence in HRT users, the stronger the association between unmeasured confounder and hand OA would need to be) [Appendix 7].

3.2.3 Discussion

In this nested case-control study in UK-based CPRD between 1998 and 2017, we observed women from age 45 longitudinally and assessed the association between systemic HRT and hand OA and between menopause and hand OA with both associations yielding increased risks of 32% and 42%, respectively. However, the increased risk of hand OA in HRT users compared to non-users disappeared in women with recorded menopause. The proportion of hand OA diagnoses decreased with increasing 1-year intervals after recorded menopause and, in women with a menopause record, when compared to non-users, we observed a 28% decreased risk of hand OA if HRT was initiated around menopause and used continuously.

Due to heterogeneous methods, a comparison of our results to previous observational studies on the association of HRT initiation and the risk of hand OA is difficult.[65–69] The authors of previous cross-sectional studies yielded contradictory results.[65–69] They had detailed hospital-based hand OA diagnoses at hand but were unable to determine temporality of HRT use and hand OA as well as the timing of HRT use relative to menopause.[65–69] Furthermore, data of HRT exposure was collected mainly through questionnaires and did not account for timing of HRT use. We observed a 32% increased risk of hand OA in HRT users when compared to non-users, which was supported by sensitivity analyses (taking into account socio-economic status, vaginal HRT use, potential lag time of diagnosis, and case validity). However, the risk disappeared after restriction to women with recorded menopause. Other observational studies assessing the association between menopause with or without HRT use and hand OA did not yield precise results mainly due to small sample sizes.[103,104,108–111] Watt et al. performed a small study (n=82) describing the association between menopause or HRT cessation and onset of hand OA symptoms in women in a UK secondary care clinic.[112] The authors reported a median duration between HRT cessation and onset of hand OA of 6 months.[112] We observed that, among women with recorded menopause who developed

hand OA, 55% of women did so within 4 years after menopause, the same proportion was reported by Watt et al.. [112]

Women who initiated HRT shortly before/after menopause were at a reduced risk of hand OA (around 28% lower risk for women with current HRT use at the index date). We hypothesize that women who use systemic HRT to alleviate vasomotor symptoms may profit from a delayed onset or progression of hand OA, when HRT is initiated around menopause and used continuously. Thus, our results support position statements of the International Menopause Society[62] and the North American Menopause Society[63], which postulate a potential benefit of HRT on joint/ muscle pain and joint stiffness based on evidence from the well-known WHI reporting reduced arthroplasty and joint pain among unopposed HRT users[113,114], and reduced joint pain and stiffness among opposed HRT users[115], compared to non-users. Our findings among current users are mainly based upon opposed HRT users (74.9% of women used opposed HRT for ≥12 months prior to the index date). To date, there is no information on the effect of progesterone alone or in conjunction with estrogen on articular cartilage. Our results also suggest that HRT cessation may slightly increase the risk of hand OA (25% risk increase ≤18 months after cessation, based on small sample size), which may question the initial clinical benefit of HRT use. We hypothesize that hand OA onset likely expressed by hand pain is similar to spontaneous exacerbation of vasomotor symptoms after HRT cessation.[63]

A strength of this study is its large population of more than 3'000 hand OA cases among women observed longitudinally from age 45 on. Furthermore, we applied a new user design, allowing us to assess temporality of HRT use and hand OA. Moreover, we likely captured near complete HRT prescription information, as CPRD prescriptions are issued electronically by the GP. We do not know if women filled their prescriptions at the pharmacy and if they adhered to the prescribed therapy. However, of women who had HRT prescribed during follow-up, 77.4% had >1 HRT prescription recorded, suggesting that most women filled their prescriptions repeatedly, and thus likely took the medication.

A major limitation of this study is the inconsistent recording of menopause in the CPRD. However, HRT use among women with recorded menopause in our study is consistent with numbers reported among the general UK female population (around 20-40% of women who have sought medical advice on menopause used HRT over time).[55,116]

Furthermore, as only around 30% of women with recorded menopause were prescribed HRT in our study, we hypothesize that women with a menopause record in the CPRD do not only represent women with severe (post)menopausal symptoms but also women who had mild symptoms or whose menopause was recorded by chance. Therefore, our results can likely be generalized to women in the UK in peri-to-post-menopause. However, sample size of some strata in our study population was small, and results have to be confirmed before drawing causal conclusions for clinical practice. However, the decreased risk of hand OA in the stratum of women initiating HRT within 3 months before or after menopause and who were still HRT users at the index date, when compared to non-users, is unlikely entirely explained by residual confounding as suggested by the results of the array approach.

3.3 Risk of hand osteoarthritis in female new users of statins of peri-to-postmenopausal age: A sequential cohort study

The subsequent work is based on data of the following publication:

Burkard T, Hügle T, Layton JB, Glynn RJ, Bloechliger M, Frey N, Jick SS, Meier CR, Spoendlin J. **Risk of incident osteoarthritis of the hand in statin initiators: A sequential cohort study** *Arthritis Care Res (Hoboken).* 2018;70(12):1795-1805.

Please see Appendix 8.

The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research with protocol 16_092R.

3.3.1 Methods

Study design and data source

We conducted a propensity score (PS)-matched sequential cohort study using data from the UK-based CPRD. We further used CPRD-linked patient level data on socio-economic status through the use of IMD, which is available for patients living in England only.[97,98]

The PS is a mathematical construct that was introduced by Rosenbaum and Rubin in 1983 to indicate probability of exposure with the treatment of interest.[117] The PS can be used as a tool to balance covariates of exposed and unexposed patients in observational studies. The estimation of the PS is independent of the outcome as it is estimated using logistic regression (seldom machine learning algorithms) using the exposure as the dependent variable and with risk factors of the outcome and confounders as the independent variables.[118] In a subsequent "outcome model" in which the risk of an outcome associated with a certain exposure is estimated, either exposed and unexposed patients were matched on their PS, or in case of weighting or adjusting, the PS may be the only covariate in the model. That means, when using PS, confounding control happens separately from risk assessment which shall yield causal effects given four assumptions: 1) consistency (i.e. we measure what we think we measure), 2) exchangeability (i.e. there are no unmeasured confounders), 3) positivity (i.e. no patient has a zero chance to be treated or not treated), and 4) no misspecification of the PS model (i.e. the selected variables to estimate the PS yield the true probability of treatment).[119] The PS method is mainly used in cohort studies.[120]

In cohort studies, patients are observed longitudinally from exposure or non-exposure until a certain outcome occurs or until the medical record ends.[82] If all patients completed follow-up, a risk ratio is estimated by dividing cumulative incidence of exposed and unexposed.[79] If confounder adjustment is needed, risk estimation is carried out with a multivariable logistic regression analysis.[82] However, if patients are censored along the way, an incidence rate ratio is estimated which takes into account contributed person-time at risk of patients. Incidence rate ratios are estimated by dividing the IR of the outcome of exposed patients by the IR of the outcome of unexposed patients.[79,99] If confounder adjusting is needed, risk estimations are carried out using Poisson regression.[82,83] A different approach taking censoring of patients into account is to define the outcome as "time-to-event" and to estimate hazard ratios (HR, crude or adjusted) in Cox proportional hazard regression analysis[121].[82]

Study population

We identified all women aged 45 to 64 years at any time between January 1996 and December 2015 in the CPRD and extracted their statin initiation episodes (those with ≥1 new prescription for atorvastatin, fluvastatin, pravastatin, rosuvastatin, or simvastatin) after a statin-free period of ≥3 years. New user designs rule out the risk of prevalent user bias, which occurs when comparing patients who have been treated with a drug for a long time to patients newly starting a drug. When compared to a patient newly starting a drug, prevalent users may be less susceptible to side effects, and therefore more adherent to the drug still being prescribed as they have not yet developed any side effects. Therefore, prevalent and new users likely differ and their comparison would introduces bias into the study.

We categorized women into one of ten 2-year entry blocks (EB) according to the date of the first prescription (referred to as cohort entry). Within each EB, we identified all women who had no statin prescriptions but had ≥3 years of recorded statin-free active history and ≥1 recorded GP encounters during the respective EB to ensure database activity. These women were assigned a random entry date within the respective EB (cohort entry) [Figure 12]. Women could only contribute one episode (statin initiation or non-initiation) per EB, but they could contribute multiple episodes throughout the study period in different EBs if eligibility criteria were fulfilled (i.e. follow-up time was counted multiple times for some women). We subsequently refer to women as statin initiators or non-initiators (which do not refer to unique women but to statin initiation episodes and non-initiation episodes).

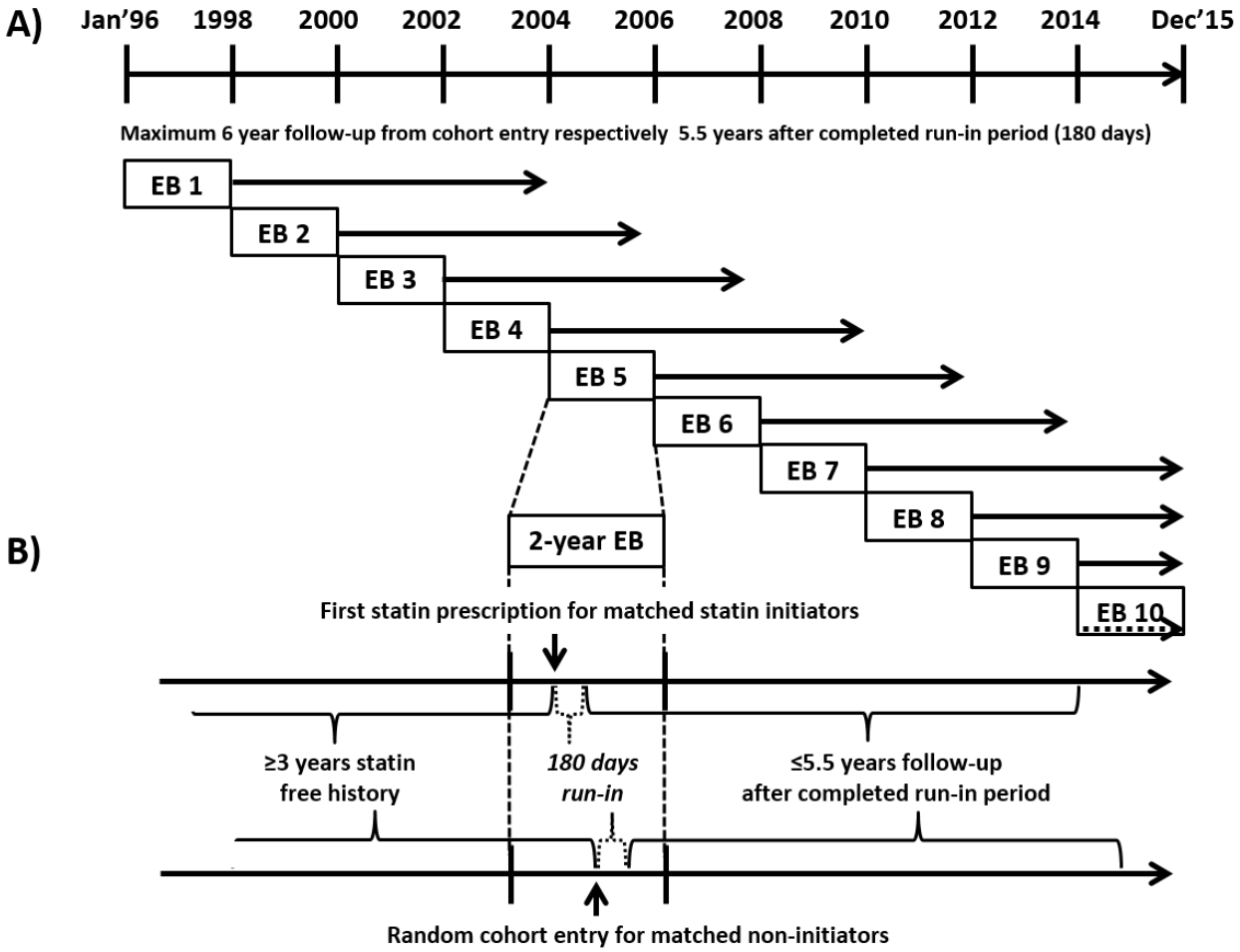

Fig12. A) Study overview. Each entry block (EB) represented one cohort. The cohorts contained all eligible statin initiators and their 1:1 propensity score‐matched non-initiators. We followed all statin initiators and non-initiators for a maximum of 6 years after their entry in an EB, respectively 5.5 years after completed run-in period until they had a record of hand osteoarthritis or they were censored.
B) Entry block in detail. At least three years statin free history was required for both statin initiators and non-initiators to enter the cohort, non-initiators required additionally ≥1 general practitioner encounters during the respective EB. Matched statin initiators entered on the date of their first statin prescription; matched non-initiators entered on a random date. After a run-in period of 180 days, all statin initiators and non-initiators were followed-up for a maximum of 5.5 years until they had a record of hand osteoarthritis or they were censored

We excluded women with a Read code for prior atherothrombotic events in favor of homogeneity of the study population (i.e. to focus on statin use for primary prevention), but also because atherothrombotic events are a clear indication to initiate a statin and patients who did not do so are likely a biased comparator group.[122] Women with strong risk factors for hand OA, such as a pre-existing OA of any joint, a disease associated with secondary OA, or a differential diagnosis of hand OA were excluded to minimize outcome misclassification. We

excluded women with alcoholism/ substance abuse, HIV/AIDS or a malignant cancer because these women are generally associated with a higher risk of bias and confounding in observational studies. Women with a previous prescription for cerivastatin (withdrawn from the market in 2001)[123] were also excluded.

PS matching

We estimated a PS (probability of statin initiation) for each statin initiator and non-initiator using multivariable logistic regression. We included characteristics recorded at any time before cohort entry, either associated with the risk of developing hand OA only, or potential confounders of the association between statin initiation and hand OA (selected a priori based on clinical knowledge) [Table 3].[124] Pre-matching enrolment duration in the CPRD prior to the index date was comparable in PS-matched statin initiators and non-initiators with a mean duration of 3.2 years (standard deviation: 2.1 years) in initiators and of 3.3 years (standard deviation: 1.9 years) in non-initiators. Covariates included comorbidities that may influence prescribing behavior (e.g. heart diseases, diabetes)[125] and proxies for healthcare seeking behavior (e.g. number of GP encounters ≤1 year prior to cohort entry).[126] To maximize comparability between matched pairs, we matched non-initiators to statin initiators within each of the ten EBs separately (accounting for time-related bias due to changing statin prescribing patterns).[127] A greedy 5-1 digit matching algorithm without replacement was applied, excluding those who could not be matched.[128]

In a sensitivity analysis, we trimmed our study population asymmetrically at the extreme ends of the PS tail (statin initiators below the 5th and non-initiators above the 95th percentile before matching) to exclude statin initiators and non-initiators treated contrary to prediction.[129,130]

Follow-up

Follow-up started on day 181 after cohort entry (Figure 12B) to allow statin initiators to reach maintenance dose and to account for the delay in diagnosis due to slow disease progression of hand OA (i.e. to reduce the probability of detecting prevalent hand OA cases during early follow-up). Exclusion of episodes of ≤180 days of follow-up also rule out inclusion of women with poor statin adherence; it has previously been shown that a large proportion of patients discontinue statin treatment shortly after the first prescription.[130,131] We followed statin initiators and non-initiators in an “as-treated” approach until the first occurrence of a

diagnosis of hand OA or censoring due to: onset of an exclusion criterion described above, change of exposure status, disenrollment from the CPRD, December 2015, or maximum follow-up of 5.5 years after completed run-in period.

In a sensitivity analysis, we started follow-up at day 1 after cohort entry.

Exposure ascertainment

We defined continuous statin exposure during follow-up based on the estimated duration of supply of each recorded statin prescription, accounting for the number of tablets and dose instructions. A statin initiator was considered continuously exposed if a subsequent prescription was recorded ≤180 days after the alleged end of supply; if not, censoring occurred at the last day of supply of the last prescription. Where prescription duration and/or dosing instructions were not recorded, we assumed a 28-day supply (mode for statin prescriptions) and a regimen of 1 tablet/day, respectively.

Statins inhibit HMG-CoA-reductase, an enzyme in liver cells involved in cholesterol biosynthesis. The resulting decrease in cholesterol synthesis leads to an increase in LDL receptors on liver cells and therefore to an increased internalization of LDL and reduced serum LDL levels.[132] Furthermore, certain statins were reported to inhibit IL-1 and MMPs involved in cartilage degradation in an articular cell culture.[133]

Outcome

We defined hand OA as the first recorded diagnosis of hand OA (base of thumb OA and hand pain were not considered).

We performed a sensitivity analysis restricted to hand OA diagnoses that were preceded by diagnostic work up (MRI, radiography, ultrasonography) or a referral/discharge to/from a rheumatologist, orthopedist, or radiologist within 180 day before the first diagnosis. Other hand OA Read codes led to censoring on the date of the hand OA diagnosis.

In a further sensitivity analysis, to account for heterogeneity by delayed hand OA diagnoses, we shifted the first hand OA diagnosis to 180 days prior to the first recorded diagnosis. Therefore, given the run-in period of 180 days, cases with less than 360 days of initial follow-up were disregarded.

To further assess the validity of our findings with respect to surveillance bias (differential healthcare seeking behavior) and the influence of unmeasured menopause onset, we defined two negative control outcomes (psoriasis and tinnitus). Negative control outcomes are not causally associated with the exposure, but should be subject to the same potential source of measured and unmeasured confounding as the original outcome.[134] Therefore, if exposure and negative control outcome yield a positive or negative association, confounding is detected.[135] If there is no association between exposure and negative control outcome, it supports the main study findings. However, it does not imply that the observed primary association is causal nor is it a test for complete absence of confounding or bias in the primary association.[135] Psoriasis and tinnitus are more likely diagnosed in patients who show healthcare seeking behavior (patients who see their GP often for minor reasons). Psoriasis was reported to exacerbate with menopause yielding increased new onset proportions in women aged 45-55 years[136] which is supposedly due to the effect of low estrogen levels on the adaptive immune system.[137] Thereby, psoriasis as a negative control outcome may disclose differential distribution of menopause among statin initiators and non-initiators.

In a secondary analysis, we assessed generalized OA as the study outcome. We did not assess generalized OA as a primary outcome due to limited capability to define generalized OA in CPRD data.[2]

Statistical analysis

After combining all sequential cohorts into one, we compared covariate distribution between treatment groups before and after PS-matching. We performed Cox proportional hazard analyses estimating HRs with 95% CI for the association of hand OA and generalized OA separately with statin initiation, compared to non-initiation. The proportional hazard assumption was tested using the martingale residual method[138] (held true overall, if hazards are proportional over time, the overall risk estimate is true throughout follow-up). For comparative reasons, we also ran all analyses using multivariable Cox regression in the unmatched cohort, adjusting for all covariates included in the PS. We performed subgroup analyses by age (45–54 years, 55-64 years), and diagnosed pre-existing dyslipidemia (i.e. a Read code of dyslipidemia or corresponding laboratory values), for which we re-matched within subgroups. We further quantified time-specific HRs within intervals of follow-up (0-1 year, 2–3 years, 4–5.5 years), excluding those whose follow-up ended before the period

of interest. The association between statin initiation and negative control outcomes was assessed identically. We further estimated pre- and post-matching c-statistics using a logistic regression model including all covariates included in the PS. The c-statistic indicates the level of covariate balance between study groups where 0.5 indicates perfect balance and 1.0 indicates maximal imbalance.[139] To assess potential confounding by socio-economic status, we performed a sensitivity analysis in patients with information on IMD only (66.4%). Therein, we added IMD as an ordinal variable (where quintile 1 represents least deprived and quintile 5 most deprived) into the PS estimation model (re-matched patient characteristics are displayed in Appendix 9). In the unmatched cohort, we added IMD as an ordinal variable into the Cox regression model. We performed all analyses using SAS statistical software version 9.4 (NC, USA).

3.3.2 Results

We identified 80,697 statin initiators (78,634 unique women [97.4%]) and 2,730,961 non-initiators (786,111 unique women [28.8%]); a total of 18,531 statin initiators (23.0%) and 160,530 non-initiators (5.9%) were further excluded due to ≤180 days of follow-up, resulting in 62,166 statin initiators and 2,570,431 non-initiators (PS distribution before PS-matching can be seen in Figure 13). Before PS-matching, the c-statistic was c=0.91.

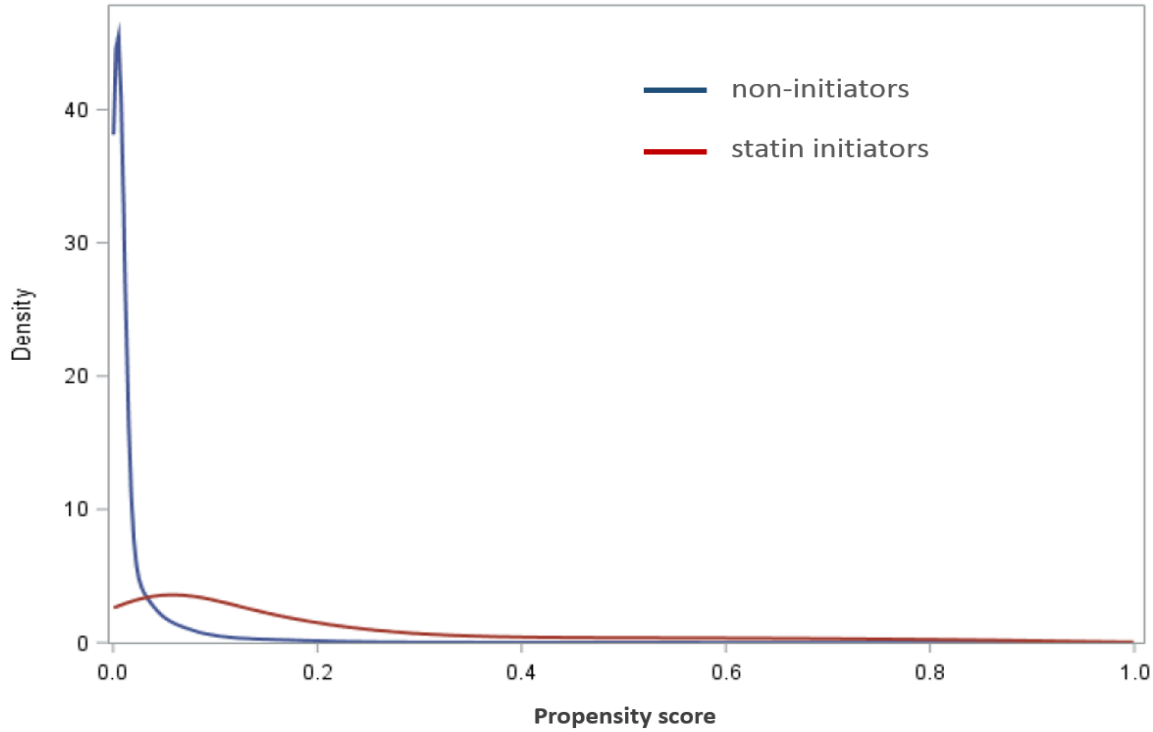

Fig13. Propensity score distribution of statin initiators and non-initiators before propensity score matching

Of the 62,166 statin initiators, 96.1% were matched to non-initiators, resulting in 59,731 PS-matched pairs (59,241 unique women in statin initiators [99.2%] and 50,527 unique women in non-initiators [81.2%]). Before PS-matching, the average age of statin initiators was higher, and statin initiators had on average shorter follow-up (mainly due to differential censoring for change in exposure status) and were more frequently hospitalized, rather obese, and more frequently diagnosed with hypertension, type2 diabetes, or heart diseases (Table 3). After PS-matching, covariate balance was achieved across all included covariates with a post-matching c-statistic of c=0.54.

Tab3. Baseline characteristics of statin initiators and non-initiators (follow-up >180 days) before and after propensity score-matching

	Before PS-matching		PS-matched	
	Statin initiators (N=62,166)	**Non-initiators (N=2,570,431)**	**Statin initiators (N=59,731)**	**Non-initiators (N=59,731)**
Mean age in years (SD)	56.3 (5.3)	53.1 (5.6)	56.3 (5.3)	56.3 (5.3)
Mean follow-up in years (SD)	3.2 (2.1)	3.8 (1.9)	3.2 (2.1)	3.3 (1.9)
Mean number of GP contacts ≤1 year before cohort entry* (SD)	19.3 (12.1)	9.8 (9.6)	18.9 (11.9)	19.6 (14.1)
Current smokers	14,780 (23.8%)	514,341 (20.0%)	14,238 (23.8%)	14,151 (23.7%)
Average alcohol intake (>14 units/week)	1915 (3.1%)	75,322 (2.9%)	1867 (3.1%)	2071 (3.5%)
Comorbidities before cohort entry:				
Obesity (BMI>30kg/m^2)	23,776 (38.3%)	502,313 (19.5%)	22,285 (37.3%)	22,735 (38.1%)
Osteoporosis†	1688 (2.7%)	46,873 (1.8%)	1625 (2.7%)	1811 (3.0%)
Dyslipidemia‡	47,156 (75.9%)	453,181 (17.6%)	44,793 (75.0%)	46,418 (77.7%)
Angina pectoris	3453 (5.6%)	18,371 (0.7%)	3066 (5.1%)	2641 (4.4%)
Type2 diabetes	11,627 (18.7%)	24,018 (0.9%)	9710 (16.3%)	8330 (14.0%)
Hypertension	29,074 (46.8%)	349,154 (13.6%)	27,574 (46.2%)	28,882 (48.4%)
Ischemic heart disease	2418 (3.9%)	6850 (0.3%)	2093 (3.5%)	1653 (2.8%)
Congestive heart failure	390 (0.6%)	2474 (0.1%)	346 (0.6%)	321 (0.5%)
Hypothyroidism	6913 (11.1%)	152,437 (5.9%)	6582 (11.0%)	7163 (12.0%)
Vascular disease	1612 (2.6%)	32,419 (1.3%)	1514 (2.5%)	1527 (2.6%)
Chronic kidney disease	1579 (2.5%)	13,939 (0.5%)	1514 (2.5%)	1507 (2.5%)
Hip fracture	176 (0.3%)	6858 (0.3%)	171 (0.3%)	182 (0.3%)
Liver disease	438 (0.7%)	6206 (0.3%)	414 (0.7%)	417 (0.7%)
COPD‡	1397 (2.3%)	24,846 (1.0%)	1310 (2.2%)	1395 (2.3%)
Deep vein thrombosis	969 (1.6%)	24,366 (1.0%)	928 (1.6%)	1054 (1.8%)
Dysphagia	1029 (1.7%)	26,989 (1.1%)	989 (1.7%)	1079 (1.8%)
≥1 hospitalization ≤1 year before cohort entry (SD)	9991 (16.1%)	229,669 (8.9%)	9508 (15.9%)	9898 (16.6%)
Incontinence	2123 (3.4%)	53,568 (2.1%)	2023 (3.4%)	2178 (3.7%)
Pneumonia	1275 (2.1%)	49,178 (1.9%)	1221 (2.0%)	1341 (2.3%)
Psychotherapy§	3759 (6.1%)	116,496 (4.5%)	3612 (6.1%)	3896 (6.5%)
Co-medication ≤180 days before cohort entry:				
Hormone replacement therapy	10,800 (17.4%)	442,297 (17.1%)	10,437 (17.5%)	11,133 (18.6%)
Oral corticosteroids	2530 (4.1%)	62,159 (2.4%)	2400 (4.0%)	2490 (4.2%)
Opioids	4224 (6.8%)	84,542 (3.3%)	3989 (6.7%)	4217 (7.1%)

Benzodiazepines	4412 (7.1%)	114,511 (4.5%)	4215 (7.1%)	4617 (7.7%)
COPD[ll] drugs	700 (1.1%)	12,156 (0.5%)	660 (1.1%)	679 (1.1%)
Coronary vasodilators	3247 (5.2%)	7504 (0.3%)	2788 (4.7%)	2170 (3.6%)
Histamin-2 antagonists	1616 (2.6%)	36,414 (1.4%)	1518 (2.5%)	1670 (2.8%)
SSRIs	6263 (10.1%)	166,375 (6.5%)	6006 (10.1%)	6356 (10.6%)
Other lipid lowering agents	1045 (1.7%)	4697 (0.2%)	976 (1.6%)	954 (1.6%)
Number of CV drugs[¶]: 0	22,449 (36.1%)	2,175,920 (84.7%)	22,429 (37.6%)	22,909 (38.4%)
Number of CV drugs[¶]: 1-3	33,659 (54.1%)	375,260 (14.6%)	32,193 (53.9%)	31,215 (52.3%)
Number of CV drugs[¶]: 4-12	6058 (9.7%)	19,251 (0.8%)	5109 (8.6%)	5607 (9.4%)

SD: standard deviation, GP: general practitioner, IMD: index of multiple deprivation, COPD: chronic obstructive pulmonary disease, SSRI: serotonin reuptake inhibitor, CV: cardiovascular PS: propensity score

* only records on separate days

† defined as an osteoporosis diagnose or intake of drugs affecting bone metabolism

‡ defined as either an hyperlipidemia Read code, a laboratory value of low density lipoprotein >3 mmol/l, of high density lipoprotein <1 mmol/l, or of triglycerides >1.7 mmol/l

§ as a proxy for psychiatric disease

ll defined as xanthines, long-acting inhaled anticholinergics including combinations, indacaterol, or aclidinium including combinations

¶ defined as ACE-inhibitors, ATII-inhibitors, beta-blockers, calcium-channel-blockers, diuretics, thrombocyte-aggregation-inhibitors, vitamin K antagonists, acetylsalicylic acid, other lipid lowering agents, insulin, oral antidiabetics, or antiarrhythmics

Censoring was comparable between statin initiators and non-initiators after PS-matching (Table 4).

Tab4. Censoring reasons before and after propensity score-matching

	Before PS-matching		PS-matched	
	Statin initiators (n=62,166)	**Non-initiators (n=2,570,431)**	**Statin initiators (N=59,731)**	**Non-initiators (N=59,731)**
Osteoarthritis	4059 (3.2%)	121,861 (4.7%)	3820 (6.4%)	3610 (6.0%)
Rheumatoid arthritis, other arthritis	955 (1.5%)	35,651 (1.4%)	893 (1.5%)	1047 (1.8%)
Crystal arthropathies	7 (0.0%)	281 (0.0%)	6 (0.0%)	6 (0.0%)
Disorders of iron metabolism	17 (0.0%)	711 (0.0%)	17 (0.0%)	21 (0.0%)
Gout	516 (0.8%)	7638 (0.3%)	488 (0.8%)	419 (0.7%)
Hem – or hydrarthoris	7 (0.0%)	180 (0.0%)	6 (0.0%)	5 (0.0%)
Hyperparathyroidism	86 (0.1%)	1792 (0.1%)	80 (0.1%)	61 (0.1%)
Wilson disease, acromegaly, or hypermobility syndrome	9 (0.0%)	407 (0.0%)	9 (0.0%)	5 (0.0%)
Previous finger injury	174 (0.3%)	8547 (0.3%)	167 (0.3%)	214 (0.4%)
Finger malformation/misalignment	534 (0.9%)	14,310 (0.6%)	497 (0.8%)	411 (0.7%)
Amputation of at least wrist level	3 (0.0%)	95 (0.0%)	3 (0.0%)	1 (0.0%)
Cancer except non-melanoma skin cancer	1854 (3.0%)	74,968 (2.9%)	1768 (3.0%)	2000 (3.4%)
HIV/AIDS	0 (0.0%)	82 (0.0%)	0 (0.0%)	0 (0.0%)
Alcohol/ other substance abuse	781 (1.3%)	29,647 (1.2%)	736 (1.2%)	724 (1.2%)
Prescription of cerivastatin	101 (0.2%)	1613 (0.1%)	97 (0.2%)	79 (0.1%)
Change of exposure status	15,135 (24.4%)	181,751 (7.0%)	14,649 (24.5%)	12,991 (21.8%)
Loss to follow-up	16,643 (26.8%)	969,827 (37.7%)	16,317 (27.3%)	19,748 (33.1%)
Completed follow-up, end of the study period	20,756 (33.4%)	1,103,140 (42.9%)	19,680 (33.0%)	17,731 (29.7%)
Death	214 (0.3%)	6506 (0.3%)	191 (0.3%)	363 (0.6%)

PS: propensity score, HIV/AIDS: human immunodeficiency virus/ acquired immune deficiency syndrome

Overall, hand OA was not associated with statin initiators with a HR of 1.07 (95% CI 0.91-1.25) compared to non-initiators (Table 5).

Tab5. Results of the association of statin initiation and incident hand osteoarthritis overall and in subgroups

	Before PS-matching				PS-matched		
	Obs. time* in statin init. + non-init.	**Hand OA events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs. time* in statin init. + non-init.**	**Hand OA events**	**HR matched† (95% CI)**
Overall	201.2+ 9783.5	11,758	1.36 (1.21-1.52)	1.16 (1.02-1.30)	192.2+ 198.0	606	1.07 (0.91-1.25)
Age in years							
45-54	69.9+ 6073.0	6466	1.38 (1.13-1.68)	1.18 (0.96-1.46)	66.2+ 71.7	187	1.17 (0.87-1.55)
55-64	131.3+ 3710.5	5292	1.22 (1.06-1.39)	1.15 (0.99-1.33)	125.0+ 125.3	401	1.10 (0.90-1.34)
Indication for statin initiation							
Present dyslipidemia	151.3+ 1395.3	2332	1.15 (1.01-1.31)	1.21 (1.05-1.39)	142.1+ 143.7	497	1.05 (0.88-1.25)
Absent dyslipidemia	49.9+ 8388.1	9426	1.03 (0.79-1.34)	1.00 (0.76-1.30)	49.5+ 53.1	123	0.90 (0.63-1.28)
Duration of follow-up							
0-1 years	54.5+ 2412.6	2566	1.30 (1.03-1.64)	1.04 (0.81-1.33)	52.3+ 55.0	152	0.92 (0.67-1.27)
2-3 years	80.1+ 3917.9	4494	1.53 (1.29-1.81)	1.29 (1.07-1.55)	76.5+ 81.5	238	1.33 (1.03-1.71)
4-5.5 years	66.6+ 3453.0	4698	1.22 (1.01-1.48)	1.10 (0.89-1.35)	63.4+ 61.5	216	0.93 (0.72-1.22)
Sensitivity analyses							
Outcome validity‡	201.2+ 9783.5	1344	1.31 (0.94-1.83)	0.98 (0.68-1.40)	192.2+ 198.0	76	0.88 (0.56-1.39)
Trimmed population§	192.0+ 9351.3	11,071	1.39 (1.24-1.56)	1.13 (1.00-1.29)	75.4+ 85.7	282	0.96 (0.76-1.21)
Outcome shift‖	199.3+ 9744.7	10,462	1.36 (1.20-1.53)	1.17 (1.03-1.33)	189.7+ 185.0	523	1.03 (0.87-1.22)
No run-in period¶	235.7+ 11,090.8	13,069	1.30 (1.17-1.44)	1.09 (0.97-1.22)	224.1+ 277.3	734	1.02 (0.88-1.17)
Additionally controlled for IMD#	127.2+ 6493.5	7912	1.37 (1.19-1.57)	1.15 (0.99-1.34)	121.0+ 125.4	395	1.01 (0.82-1.24)

IMD: index of multiple deprivation, PS: propensity score, Obs.: observation, init.: initiators, non-init.: non-initiators, OA: osteoarthritis

* Observation time in 1'000 person-years

† Hazard ratio adjusted for/ PS estimation with all covariates (Table 3)

‡ Only including hand osteoarthritis diagnoses that were preceded by diagnostic work up (MRI, radiography, ultrasonography) or a referral/discharge to/from a rheumatologist, orthopedist, or radiologist within 90 day before or after the first diagnosis

§ Study population trimmed asymmetrically at the extreme ends of the propensity score (at the 5th percentile in exposed and at the 95th percentile in unexposed)

‖ hand osteoarthritis diagnoses shifted to 180 days before the initial record in the CPRD

¶ follow-up started at day 1 instead of at day 181

in patients with information on index of multiple deprivation only (re-matched patient characteristics in Appendix 9). Index of multiple deprivation was used as an ordinal variable where quintile 1 represents least deprived and quintile 5 most deprived.

All sensitivity analyses also yielded overall null results (proportional hazard assumption did not hold in sensitivity analysis without run-in period as survivor functions crossed at around year 3 of follow-up). There was a slightly increased risk of hand OA in statin initiators with a follow-up of 2-3 years (1.33, 95% CI 1.03-1.71). Other subgroups (age and indication for statin initiation) yielded null results. Our results of the multivariable and PS-matched analyses were similar except in the stratum of present dyslipidemia (adjusted HR of 1.21, 1.05-1.39, matched HR of 1.05, 95% CI 0.88-1.25).

The outcome generalized OA was not associated with statin initiation in the overall PS-matched cohort (HR 0.98, 95% CI 0.82-1.17) nor in any subgroup except for the subgroup of women aged 55-64 years (HR 1.31, 95% CI 1.05-1.62) [Table 6]. Results of the multivariable and PS-matched analyses were similar.

Tab6. Results of the association of statin initiation and incident generalized osteoarthritis overall and in subgroups

	Before PS-matching				PS-matched		
	Obs. time* in statin init. + non-init.	**Gener. OA events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs. time* in statin init. + non-init.**	**Gener. OA events**	**HR matched† (95% CI)**
Overall	212.5+ 10,123.4	6977	1.83 (1.61-2.07)	1.15 (1.00-1.32)	203.2+ 208.1	494	0.98 (0.82-1.17)
Age in years							
45-54	73.1+ 6236.8	3317	1.71 (1.34-2.19)	0.96 (0.73-1.27)	69.0+ 74.7	127	0.94 (0.66-1.33)
55-64	139.5+ 3886.6	3660	1.55 (1.34-1.79)	1.25 (1.06-1.47)	133.1+ 132.9	328	1.31 (1.05-1.62)
Indication for statin initiation							
Present dyslipidemia	159.9+ 1454.0	1331	1.48 (1.27-1.73)	1.15 (0.98-1.37)	150.4+ 150.6	324	1.16 (0.93-1.44)
Absent dyslipidemia	52.7+ 8669.4	5646	2.03 (1.59-2.57)	1.18 (0.92-1.52)	52.1+ 56.0	128	1.18 (0.84-1.68)
Duration of follow-up							
0-1 years	55.5+ 2438.9	1346	1.80 (1.37-2.37)	1.11 (0.82-1.49)	53.3+ 56.0	115	0.81 (0.56-1.17)
2-3 years	83.9+ 4029.8	2716	2.03 (1.68-2.46)	1.28 (1.04-1.58)	80.3+ 85.1	203	1.18 (0.90-1.56)
4-5.5 years	73.1+ 3654.7	2915	1.65 (1.34-2.03)	1.06 (0.84-1.33)	69.6+ 67.1	176	0.90 (0.67-1.21)

PS: propensity score, Obs.: observation, init.: initiators, non-init.: non-initiators, Gener.: generalized, OA: osteoarthritis
* Observation time in 1'000 person-years
† Hazard ratio adjusted for / PS estimation with all covariates (Table 3)

The negative control outcomes psoriasis and tinnitus were neither associated with statin use overall nor in any subgroup (Table 7/8).

Tab7. Results of the association of statin initiation and incident psoriasis overall and in subgroups

	Before PS-matching				PS-matched		
	Obs. time* in statin init. + non-init.	**Psoria. events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs. time* in statin init. + non-init.**	**Psoria. events**	**HR matched† (95% CI)**
Overall	290.1+ 11,920.7	21,711	1.32 (1.23-1.43)	0.99 (0.91-1.08)	278.2+ 282.9	1270	1.04 (0.93-1.16)
Age in years							
45-54	90.8+ 6954.7	11,955	1.50 (1.32-1.71)	1.05 (0.91-1.21)	86.1+ 92.5	433	1.02 (0.84-1.23)
55-64	199.3+ 4966.0	9756	1.20 (1.09-1.32)	0.98 (0.88-1.08)	190.64+ 189.1	830	1.02 (0.89-1.17)
Indication for statin initiation							
Present dyslipidemia	218.7+ 1832.0	4336	1.10 (1.00-1.21)	0.96 (0.87-1.06)	205.9+ 204.4	907	1.02 (0.90-1.16)
Absent dyslipidemia	71.4+ 10,088.8	17,375	1.44 (1.24-1.67)	1.14 (0.98-1.33)	70.9+ 75.3	330	1.17 (0.94-1.45)
Duration of follow-up							
0-1 years	74.3+ 2847.9	5001	1.33 (1.14-1.56)	0.99 (0.84-1.17)	71.6+ 75.2	310	0.94 (0.76-1.16)
2-3 years	66.9+ 2684.8	8624	1.34 (1.18-1.51)	0.96 (0.84-1.10)	109.6+ 115.6	524	1.00 (0.84-1.19)
4-5.5 years	101.7+ 4336.3	8086	1.30 (1.14-1.48)	1.05 (0.91-1.21)	97.0+ 92.1	406	1.19 (0.96-1.45)

PS: propensity score, Obs.: observation, init.: initiators, non-init.: non-initiators, Psoria.: psoriasis

* Observation time in 1'000 person-years

† Hazard ratio adjusted for / PS estimation with all covariates (Table 3), except for hip fracture. Additionally adjusted for non-steroidal anti-inflammatory drugs, family history of psoriasis and history of organ transplantation

Tab8. Results of the association of statin initiation and incident tinnitus overall and in subgroups

	Before PS-matching				PS-matched		
	Obs. time* in statin init. + non-init.	**Tinnit. events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs. time* in statin init. + non-init.**	**Tinnit. events**	**HR matched† (95% CI)**
Overall	289.6+ 11,881.1	41,763	1.23 (1.16-1.30)	1.00 (0.94-1.06)	277.5+ 281.8	2351	0.97 (0.90-1.06)
Age in years							
45-54	91.5+ 6969.5	22,172	1.16 (1.05-1.30)	0.96 (0.85-1.08)	86.7+ 92.6	672	0.96 (0.83-1.12)
55-64	198.1+ 4911.5	19,591	1.16 (1.09-1.24)	1.02 (0.95-1.10)	189.1+ 186.8	1658	1.00 (0.91-1.10)
Indication for statin initiation							
Present dyslipidemia	218.3+ 1816.1	8555	1.05 (0.98-1.12)	1.03 (0.96-1.11)	205.4+ 203.6	1798	1.02 (0.93-1.12)
Absent dyslipidemia	71.3+ 10,064.9	33,208	1.07 (0.94-1.21)	0.95 (0.84-1.08)	70.7+ 75.4	525	0.94 (0.79-1.12)

	Before PS-matching				PS-matched		
	Obs. time* in statin init. + non-init.	Tinnit. events	HR crude (95% CI)	HR adjusted† (95% CI)	Obs. time* in statin init. + non-init.	Tinnit. events	HR matched† (95% CI)
Duration of follow-up							
0-1 years	74.4+	9427	1.29	1.02	71.6+	601	1.00
	2847.1		(1.15-1.44)	(0.90-1.15)	75.2		(0.85-1.17)
2-3 years	114.1+	16,241	1.25	1.00	109.4+	946	0.98
	4724.3		(1.14-1.37)	(0.91-1.11)	115.3		(0.87-1.12)
4-5.5 years	101.1+	16,095	1.16	0.99	96.4+	804	0.94
	4309.6		(1.06-1.28)	(0.89-1.10)	91.3		(0.82-1.08)

PS: propensity score, Obs.: observation, init.: initiators, non-init.: non-initiators, Tinnit.: tinnitus
* Observation time in 1'000 person-years
† Hazard ratio adjusted for / PS estimation with all covariates (Table 3) except for hip fracture. Additionally adjusted for initiation of non-steroidal anti-inflammatory drugs and anti-depressant drugs

3.3.3 Discussion

In this cohort study in the UK-based CPRD between 1996 and 2015, in women aged 45 to 64, we assessed the association between statin initiation and hand OA and between statin initiation and generalized OA. We observed that statin use was neither associated with hand OA nor with generalized OA overall. However, compared to non-initiators, in the subgroups of follow-up of 2-3 years, statin initiators yielded a 33% increased risk of hand OA and in the subgroup of women aged 55 to 64, statin initiators yielded a 31% increased risk of generalized OA.

Observed increased risks may be chance findings among the multitude of performed analyses, they may reflect true associations, or they may indicate residual confounding. The increased risks of hand OA among statin initiators with a 2-3 year follow-up was likely a chance finding because the proportional hazards assumption held true overall, which implies that hazards among statin initiators and non-initiators were sufficiently constant throughout follow-up. Moreover, the proportional hazard assumption in the sensitivity analysis without a run-in period did not hold true. The survivor functions showed a separation of hazards right at the start of follow-up with a lower hazard of hand OA among statin initiators and crossed in year 3 of follow-up. The finding of this sensitivity analysis indicates that including women from day 1 of follow-up may have introduced bias into the study as an immediate effect of statins on hand OA would be unlikely and early discontinuers of statins likely differ from those remaining on statin therapy in dyslipidemia severity for example.

The increased risk of generalized OA in women aged 55 to 64 years old likely indicates residual confounding as we observed consistently increased crude HRs for the association between statin initiation and generalized OA. The finding may be due to post-menopausal women rather having dyslipidemia than premenopausal (younger) women and that statin initiation may be a proxy for more severe dyslipidemia for which we could not adequately control. Dyslipidemia as a risk factor for hand OA may not have been either adequately controlled for in multivariable adjusted models yielding an increased HR of hand OA in statin initiators compared to non-initiators overall and with present dyslipidemia (the risk disappeared in the PS-matched cohort). Our results of the multivariable and PS-matched analyses were similar among all other subgroups and results of all sensitivity analyses supported the robustness of our methodology.

It is known that the lack of a suitable active comparator group imposes several challenges when studying statins in large electronic databases, because non-initiators may inherently differ from statin initiators in ways that are not captured electronically. For example, maintenance of statin therapy positively correlates with increased healthcare utilization and positive health-related behaviour,[126] whereas comorbidities predict decreased statin adherence.[125] Furthermore, non-adherence is not possible in non-users, which can lead to differential censoring. To address these challenges, we introduced negative control outcomes to control for residual confounding by healthcare utilization (surveillance bias). Observed null results throughout the PS-matched cohort in both negative control outcome analyses suggest that surveillance bias did not play a major role in this study. Furthermore, menopause as a major risk factor for hand OA was likely adequately controlled for as use of HRT and SSRIs, osteoporosis (and hip fracture), incontinence, and dyslipidemia were balanced after PS-matching potentially indicating menopause. Moreover, the negative control outcome psoriasis did not disclose a potential differential distribution of menopause between statin initiators and non-initiators.

We did not include a robust estimator in our model due to computational power restrictions, although women may have entered our cohort multiple times. However, inclusion of a robust variance estimator in overall analysis of hand OA in all statin initiators widened CIs by a maximum of 0.01. Pre- and post-matching c-statistics showed strongly increasing covariate balance with increasing levels of restriction of the study population with almost perfect

balance (of measured covariates) after PS-matching (c=0.54), supporting our decision to apply the chosen restrictions and PS matching. HRT use was already balanced among groups pre-matching and yielded a slightly higher percentage among non-initiators than among statin initiators post-matching. However, given potential confounding by menopause (statin initiators being more likely postmenopausal as dyslipidemia is more prevalent among postmenopausal women than among premenopausal women), the slight imbalance in HRT use would have introduced bias towards the null. Moreover, given the strict inclusion criteria and PS-matching applied in our study, our final study population is not population-based but highly restricted to maximize comparability between study groups.

This is the first observational study evaluating the risk of hand OA in association with statin initiation among peri-to-postmenopausal women using a well-validated primary-care database and robust analytical methods. Our results suggest no effect of statins on the risk of hand OA in peri-to-postmenopausal women irrespective of age and pre-existing dyslipidemia. Additional analyses with negative control outcomes corroborate this finding.

Limitations, Conclusions and Outlook

4 Limitations, Conclusions, and Outlook

4.1 Limitations

Observational research in general is limited by the quality of the previously collected data. Especially information that was not previously collected can lead to unmeasured confounding and misclassifications which has to be considered carefully in observational epidemiology.

When assessing HRT use, menopause, or statin use in association with hand OA, an important unmeasured confounder is a patient's healthcare seeking behavior because hand OA as a non-emergency disease is more likely diagnosed in healthcare seekers. We tried to control for this confounder by controlling for the number of GP visits (prior to cohort entry), chronic diseases, or vaccine use (which are associated with healthy behavior). Additionally, we used negative control outcomes, which yielded null results throughout. A further important unmeasured confounder is socio-economic status which is measured as IMD. When controlling for quintiles of IMD in patients with information on IMD, results remained unchanged. Local estrogen concentrations in, for example, cartilage, bone, liver, and hypothalamus may be another major unmeasured confounder for which we could not control. However, their exact role in the etiology of postmenopausal symptoms and OA are not yet completely understood. Furthermore, it is unclear whether the risk factor genetic predisposition for hand OA (for which we could not control for either) is associated with postmenopausal symptoms and therefore a true confounder. Lifestyle factors as potential confounders such as smoking, BMI, or alcohol consumption were almost completely recorded among peri-to-postmenopausal women; however, stages in life such as menopause were inconsistently recorded. This is a limitation as menopause is a major risk factor of hand OA, is associated with HRT use and potentially associated with statin use. To control for menopause onset, we restricted large parts of the nested case-control analysis to women with recorded menopause. Furthermore, the CPRD contains no records of over-the-counter medicine including plant-based preparations frequently used to treat menopausal symptoms (e.g. black cohosh, red clover) or increased lipid levels (e.g. red yeast rice extract, artichoke leaf extract) or information on women's diet or physical activity, which may be confounders of the association between HRT or statin use and hand OA. Taken together, residual confounding may remain but likely not to an extent that could explain our study results.

We see prescriptions in the CPRD (electronically issued), but we do not know if women filled them at the pharmacy. Therefore, we can only assume that - in case of repeated prescriptions - the woman filled the prescription and took the medication. Information on the prescribed drug quantity is recorded in the CPRD, but occasionally shows improbably low or high values. We imputed missing values and outliers as follows: for very low values, we assumed number of packages instead of drug quantity and for very high values which would allow for continuous drug exposure over several years by one single prescription, we put previously assessed default values of the most frequently prescribed supply (i.e. mode) for this drug product. We did the same for improbable dosages; improbably low or high values were replaced with the dosage mode of all prescriptions of this drug product in the CPRD. Furthermore, we can rarely see a woman's full medical history in the CPRD, because they may not stay with a GP practice contributing data to the CPRD for their whole life. Therefore, when assessing first-time use of a drug, women may not have been true first-time users even though we required women to be present for at least 1-3 years prior to cohort entry. However, we presumed the number of misclassifications in drug use to be small as neither systemic HRT use nor statin use is often intermitted by several years. Taken together, repeated prescriptions likely reflect drug use and thus should have resulted only in little exposure misclassification.

According to NICE guideline on "Osteoarthritis: care and management", hand OA is a straight forward diagnosis mainly made in primary care without diagnostic testing or secondary care referrals. Therefore, we were not able to perform a formal validation of the hand OA outcome using diagnoses made in secondary care. Furthermore, feedback from secondary care into primary care records may be incomplete, as entries have to be entered manually, for which time may be sometimes lacking in a GP practice. However, results did not change meaningfully in sensitivity analyses with a stricter outcome definition including secondary care entries. Hand OA may be diagnosed early by chance or not until late when the disease has become debilitating. Therefore, we may have underestimated rates of incident hand OA diagnoses. However, a shift of the hand OA diagnosis by 180 days did not change results. Taken together, potential disease misclassification unlikely explains our results.

Despite these limitations, results of conducted studies in this thesis remain meaningful and are an important fundament for future research concerning clinical practice in women's mid-life health.

4.2 Conclusions

Our aim was to identify drugs potentially delaying hand OA. Observed IRs of HRT use suggest that HRT initiation can be considered a proxy for menopause before age 60. We observed IRs of HRT use and of hand OA which both increased uniformly until age 54, the age when most women experienced menopause. We further observed a positive association between menopause and hand OA and that incident hand OA proportions were highest within the first year after recorded menopause and decreased with increasing time after recorded menopause. These results underpin the existing hypothesis that menopause is a risk factor of hand OA. However, IRs of hand OA only peaked in women aged 55-59 years and remained almost constant thereafter. This suggests that menopause is not the only risk factor for hand OA because otherwise we would have expected hand osteoarthritis incidence rates to decline similarly to incidence rates of hormone replacement therapy use among older age groups.

Temporal trends of IRs of HRT use and hand OA could not confirm the hypothesis of a menopause-mediated association between HRT use and hand OA as IRs of hand OA in men also behaved inversely to IRs of HRT use over time. However, the decreased risk of hand OA in HRT users if HRT was initiated shortly before or after menopause and used continuously suggest that timely initiation of HRT around menopause may be crucial for a potential beneficial effect of HRT on hand OA. We observed consistently lower risks of hand OA in current HRT users than in past HRT users compared to non-users. Furthermore, we observed an increased risk of hand OA shortly after HRT cessation (however, statistically non-significant) which decreased with time between HRT cessation and hand OA which may be similar to a rebound effect of vasomotor symptoms after HRT cessation. These results underpin the hypothesis of a potential estrogen-mediated effect on joint tissue as estrogen receptors are present in joint tissues and estrogen was reported to inhibit TNF and MMPs involved in cartilage degradation. However, the existence of further potential mediators remains elusive. Nonetheless, HRT potentially delayed hand OA onset to after HRT cessation.

On the other hand, given observed null results of statin use and hand OA, respectively generalized OA, we are not able to rule out a potential beneficial effect of statins on OA through lipid lowering or through direct inhibition of IL-1 and MMPs as suggested by preclinical studies. However, if such effects are present, they do not seem to translate into a clinically meaningful reduction of hand OA in peri-to-postmenopausal women.

4.3 Outlook

There was a time when human life ended shortly after the reproductive period. Today, women live well beyond their reproductive age and are particularly affected by hormonal changes induced by the end of their reproductive period. Therefore, research in all aspects of this transition is needed, from vasomotor symptoms to mood changes, lipid level changes to changes in immune responses. There are few studies which have investigated serum concentrations of estrogen or progesterone in relation to postmenopausal symptoms. Yet, it is a difficult field to study because of the complex interplay between systemic factors. Notably, because local estrogen concentrations, dependent on estrogen receptor and aromatase expression, were reported to play an important role rendering serum concentrations meaningless.

Observational data from medical records can be used to assess the association between HRT or menopause and certain outcomes. However, observational research is limited due to unmeasured confounding such as menopause onset, healthcare seeking behavior, and potentially local estrogen concentrations. Randomized controlled trials represent the gold standard in assessing effects of drugs but have become unethical in the field of HRT due to reported adverse events such as breast cancer and CVD.

Large prospective cohorts observing women from age 40 or even earlier could contribute to the demystification of menopausal changes, their causes, influencing factors, and drug utilization and effectiveness aspects concerning postmenopausal symptoms relief. Thereby, hormone levels at various locations in the body as well as aromatase and estrogen receptor expressions could be regularly measured. Furthermore, core temperature, skin parameters, joint pain including imaging of affected joints, lipid levels, and serotonin levels could be measured, while comorbidities and drug intake could be observed as well. Smartphone applications could be used to collect self-reported patient information on daily symptoms, diet, mood, and physical activity for example. However, questions whether factors in young age play a role in the development of postmenopausal symptoms, or whether symptom severity is pre-determined by the genome through heredity remain.

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8 Appendix

8.1 Appendix 1

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Utilization pattern of hormone therapy in UK general practice between 1996 and 2015: a descriptive study

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Abstract

Objective: To describe the long-term trends in hormone therapy (HT) use in UK general practice after evidence of associated increased risks of cardiovascular disease (CVD) and breast cancer, subsequent guideline changes in 2003/2004 advising individualized HT prescribing, and halving of HT use between 2002 and 2005.

Methods: We conducted a descriptive study to quantify annual proportions of overall and new HT use in women aged 40 to 79 years, using the UK-based Clinical Practice Research Datalink (1996-2015). We further described HT utilization patterns (drug type, administration route, dose) within 2-year blocks overall and within subpopulations with pre-existing CVD or breast cancer.

Results: Overall HT use continued to decline from 9.4% in 2006 to 7.5% in 2015. Between 1998 and 2001, the proportion of HT initiation was around 1.7%, which halved by 2005 (0.8%), and increased again up until 2015 (1.0%). The mean age of HT users increased from 54.7 in 1996/1997 to 56.6 in 2002/2003, and leveled off at 57 to 58 years in 2014/2015. The prevalence of CVD in HT users decreased from a peak of 5.8% in 2002/2003 to 4.5% in 2014/2015, whereas breast cancer prevalence continuously increased from 0.9% in 1996/1997 to 1.9% in 2014/2015. Overall, we observed trends towards use of estrogen therapy, vaginal HT, and lower HT dose after 2002/2003, which were stronger among subpopulations with pre-existing CVD or breast cancer.

Conclusion: Our study suggests that the HT guideline changes implemented in UK clinical practice resulted in safer HT use, particularly in women with pre-existing CVD or breast cancer.

Key Words: Drug utilization – Epidemiology – Hormone therapy.

In the 1960s, synthetic hormone therapy (HT) was introduced for the treatment of postmenopausal symptoms (mainly vasomotor symptoms), and was soon seen as a remedy to preserve women's youth.[1] In addition, in the 1980s and 1990s, several observational studies reported a protective effect of HT on risk of cardiovascular diseases (CVDs), for which a causal explanation became accepted knowledge.[2-4] However, two randomized controlled trials published in the late 1990s (Heart and Estrogen/progestin Replacement Study [HERS]) and early 2000s (Women's Health Initiative [WHI]) contradicted these findings: the first reported no cardioprotective effect, and the second a slightly increased risk of CVD for oral estrogen plus progestogen (EPT, the most widely used HT).[5,6] The WHI and the Million Women Study (MWS)—a large observational study published in 2003—further reported an increased risk of breast cancer associated with oral EPT (WHI), and with any estrogen-containing therapy (ie, EPT and estrogen therapy [ET]) (MWS).[6,7] Subsequently, in 2003 and 2004, all major menopause societies (ie, The North American Menopause Society [NAMS], the International Menopause Society [IMS], and the European Menopause and Andropause Society [EMAS]) changed their guidelines on safe HT use.[8-12] They took into account all study results and provided balanced perspectives that considered study limitations (HT users were found to be systematically different from participating nonusers). Moreover, they emphasized the implications of the study findings (ie, small absolute risks: seven additional CVD cases per 10,000 women per year in the first 5 years of EPT use) rather than relative risks (ie, 29% increased CVD risk in the first 5 years of EPT use). Further, they advised individualized HT use (ie, attention to agents, administration route, dose, and length of treatment) based on important baseline risks (ie, age, lifestyle, family history of CVD, or breast cancer). Their later position papers provided further guidance on use of HT for postmenopausal symptoms by differentiating risk profiles.[13-18]

Three studies described HT use in the UK within periods between 1991 and 2010.[19-21] They found an increase in HT

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use until around 2002 and a subsequent decline until 2010.[19,20] However, none of these studies described proportion of new HT use, HT user characteristics, or use of different drug types, administration routes, or doses of HT in the general UK female population or subpopulations at high risk of first-time or recurrent CVD or breast cancer over time.

In this study, we described the long-term impact of HT use guideline changes in 2003/2004 newly advising individualized HT use based on risk profiles, by estimating overall and new HT use by year from 1996 through 2015. Furthermore, we described the impact of guideline changes on characteristics of HT users over time, and described detailed HT utilization patterns (drug types, administration routes, and estrogen doses of HT) among the general UK female population overall, and separately among subpopulations with breast cancer, CVD, or CVD risk factors.

METHODS

Study design and data source

We conducted a population-based descriptive study using data derived from Clinical Practice Research Datalink (CPRD) primary care data obtained under license from the UK Medicines and Healthcare products Regulatory Agency. Patients provide their data, which are collected by the National Health Service (NHS) as part of their care and support. The CPRD comprises this de-identified primary care data of more than 11.3 million patients.[22] General practitioners (GPs)—gatekeepers within the NHS—record information on diagnoses, prescriptions, medical symptoms, laboratory values, referrals to secondary care, demographics, and lifestyle factors (eg, BMI, smoking status) on computers.[23] Diagnoses were repeatedly shown to be of high validity.[24] We further used CPRD-linked patient-level data on Index of Multiple Deprivation (IMD), which is available for English patients only.[25,26]

The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (protocol 18_034R, made available to journal editors of this manuscript). The interpretation and conclusions contained in this study are those of the authors alone.

Study population

We identified all women aged 40 to 79 years (based on their year of birth) between January 1996 and December 2015 (study period). To capture new use of HT, we restricted the study population to women who had no HT prescriptions before age 40 (based on their year of birth), had at least 3 years of history in the database before their first HT prescription, and who had ≥1 GP contacts before the first HT prescription.

Exposure

We defined HT use as a recorded prescription for any ET, EPT (including separate ET and progestogen prescriptions prescribed within close proximity), or tibolone product, regardless of route of administration. We categorized estrogen doses of HT products (further referred to as ''doses'') according to a product's single estrogen dose strength (Supplement Digital Content [SDC] 1, http://links.lww.com/MENO/A384).[27-29]

Covariates

We described the following patient characteristics among HT users and nousers: mean age in years, mean number of GP contacts, IMD in quintiles where ''1 = least deprived'' and ''5 = most deprived'', a record of breast cancer, CVD (defined as myocardial infarction, ischemic stroke, or angina pectoris), and CVD risk factors (current smoking, obesity or BMI value >30 kg/m^2, hypertension, hyperlipidemia, or diabetes). We identified diagnoses using Read codes.[24]

Data analysis

We divided the study period into twenty 1-year blocks, and estimated the annual proportion of overall and new HT use. Proportions were estimated by dividing the number of HT users, respectively, new HT users only in each calendar-year by the total number of women aged 40 to 79 years available in the CPRD at any time during the respective year. We further stratified proportions of new users by age groups (40-49 years, 50-59 years, 60-69 years, 70-79 years) within ten 2–year blocks (ie, 1996/1997).

Also, within each of the ten 2-year blocks in the study period, we described patient characteristics of HT users and nonusers. We further described overall and detailed HT utilization patterns in subpopulations with breast cancer, CVD, or CVD risk factors, and compared findings to those in the general UK female population (including patients with breast cancer, CVD, and CVD risk factors). Detailed HT utilization patterns comprised the following strata: drug types (ET, EPT, tibolone, mixed use), administration routes (oral, vaginal [ET only], transdermal including topical, other [injection, implant, nasal], mixed use), and doses (normal dose, low dose including ultra-low dose, mixed use) (SDC 1, http://links.lww.com/MENO/A384). ''Mixed use'' refers to concomitant or consecutive use of HT products belonging to different drug types, administration routes, or doses within any 2-year block. As HT treatment options are limited for breast cancer patients, we further described HT use by combined stratification of HT drug type, administration route, and dose. Moreover, we stratified the subpopulation with CVD risk factors by number of risk factors (0-1, 2-3, 4-5) and assessed use of HT overall and in strata of different administration routes. We calculated respective proportions in HT utilization patterns among subpopulations by dividing the number of certain HT users (eg, ET users only) in each 2-year block (given certain population restrictions, eg, CVD patients only) by the total number of women aged 40 to 79 years available in the CPRD at any time during the respective 2-year block (given certain population restrictions, eg, CVD patients only). All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

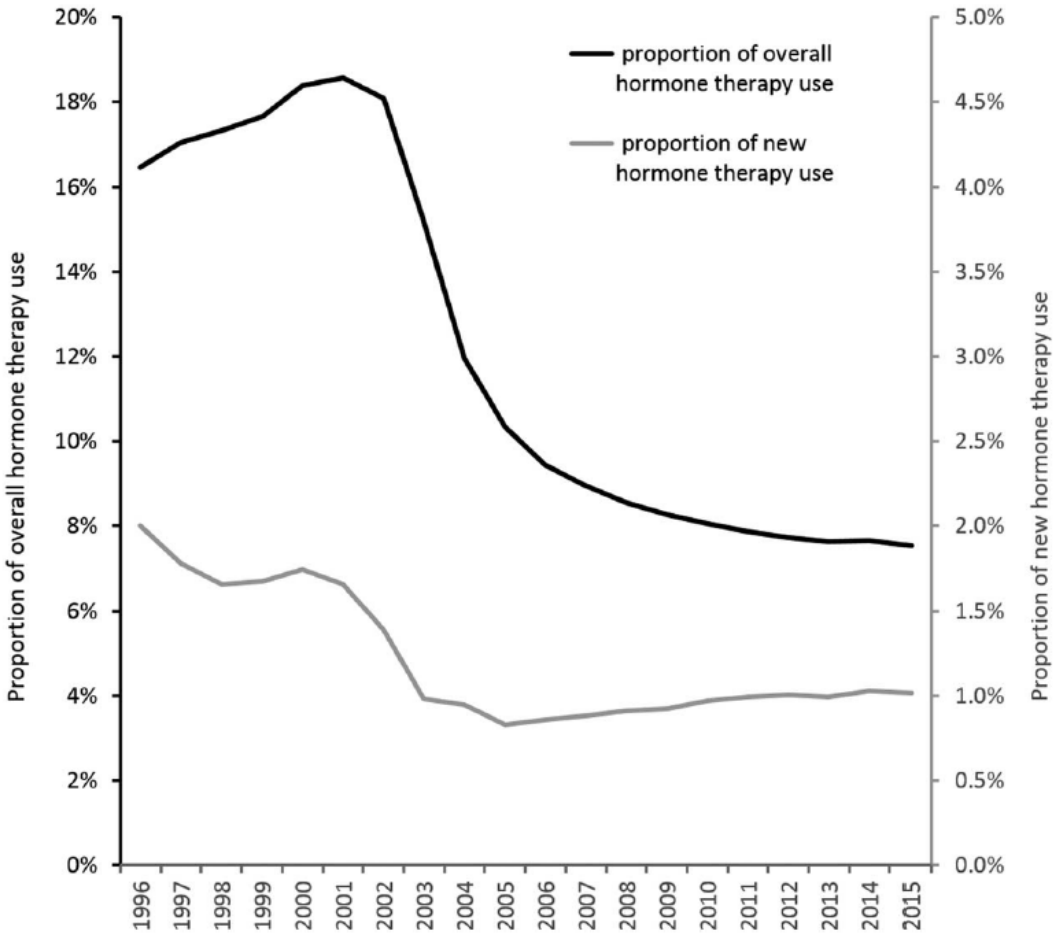

FIG. 1. Proportion of overall and new hormone therapy use in the general UK female population from 1996 to 2015. Numeric values corresponding to this figure can be found in Supplemental Digital Content 2, http://links.lww.com/MENO/A385.

RESULTS

Proportions of overall and new HT use in the general UK female population

From 1996 to 2015, among 21,218,524 women (one count for each year a woman was present), we identified 2,543,841 HT users (one count for each year a woman was prescribed HT), of whom 252,046 women met our definition of a new HT user (SDC 2, http://links.lww.com/MENO/A385). The proportion of women who received prescriptions for HT was 16.5% (142,712 HT users) in 1996, which increased to around 18% (around 195,000 HT users) between 2000 and 2002, then dropped to 10.3% (119,158 HT users) in 2005, and leveled off at 7.5% in 2015 (61,948 HT users) (Fig. 1, SDC 2, http://links.lww.com/MENO/A385). The proportion of new HT use was 2.0% (17,349 first HT prescriptions) in 1996, decreased slightly to 1.7% (17,559 first HT prescriptions) in 2001, then steeply to 0.8% (9,536 first HT prescriptions) in 2005, before slowly rising again to 1.0% (8,335 first HT prescriptions) in 2015 (Fig. 1, SDC 2, http://links.lww.com/MENO/A385). Over time, the proportion of new HT use was largest in the subgroup aged 50-59, with a maximum of 5.0% (12,363 first HT prescriptions) in 1996/1997 and a minimum of 2.3% (7,955 first HT prescriptions) in 2004/2005 (SDC 3, http://links.lww.com/MENO/A386).

Descriptive analysis of patient characteristics

Table 1 provides characteristics of HT users and nonusers over time (IMD [SDC 4, http://links.lww.com/MENO/A387]). Mean age of HT users rose from 54.7 years in 1996 to 58.7 years in 2015. Prevalence of CVD and breast cancer was lower in HT users than in nonusers throughout the study period. Mean age and prevalence of CVD and CVD risk factors converged over time in HT users and nonusers, whereas mean numbers of GP contacts and prevalence of breast cancer diverged (Graphs in SDC 5, http://links.lww.com/MENO/A388). SDC 6 (http://links.lww.com/MENO/

TABLE 1. *Main patient characteristics of hormone therapy users and nonusers from 1996/1997 to 2014/2015*

Exposure status	Years	Number of women	Mean age [y] (SD)	Mean number of GP contacts (SD)	Breast cancer (%)	CVD (%)	CVD risk factors (%)
HT users	96/97	180,034	54.7 (7.9)	21.9 (17.0)	1,633 (0.9)	9,130 (5.1)	97,189 (54.0)
	98/99	203,459	55.3 (7.9)	23.0 (17.9)	1,999 (1.0)	10,799 (5.3)	114,983 (56.5)
	00/01	226,176	55.8 (7.9)	25.2 (19.3)	2,449 (1.1)	12,449 (5.5)	135,204 (59.8)
	02/03	218,882	56.6 (7.9)	27.9 (21.2)	2,780 (1.3)	12,693 (5.8)	139,837 (63.9)
	04/05	156,313	56.9 (8.2)	32.6 (24.3)	2,380 (1.5)	8,591 (5.5)	105,207 (67.3)
	06/07	132,624	57.1 (8.5)	35.2 (26.1)	2,289 (1.7)	6,862 (5.2)	90,398 (68.2)
	08/09	120,734	57.5 (8.8)	38.4 (28.0)	2,214 (1.8)	6,050 (5.0)	82,955 (68.7)
	10/11	112,636	57.8 (8.9)	39.7 (29.1)	2,102 (1.9)	5,441 (4.8)	77,106 (68.5)
	12/13	102,821	58.1 (9.0)	41.7 (30.4)	2,066 (2.0)	4,852 (4.7)	70,899 (69.0)
	14/15	87,413	58.3 (9.0)	40.8 (31.1)	1,651 (1.9)	3,933 (4.5)	60,487 (69.2)
Nonusers	96/97	778,763	58.1 (12.2)	16.3 (16.6)	17,601 (2.3)	59,648 (7.7)	384,578 (49.4)
	98/99	842,335	57.9 (12.4)	17.4 (17.6)	20,917 (2.5)	65,566 (7.8)	436,423 (51.2)
	00/01	893,320	57.4 (12.3)	19.1 (19.3)	24,437 (2.7)	68,824 (7.7)	490,062 (54.9)
	02/03	956,980	56.9 (12.2)	20.8 (20.9)	27,893 (2.9)	70,826 (7.4)	560,143 (58.5)
	04/05	1,063,195	56.6 (11.9)	24.1 (23.3)	32,391 (3.1)	73,486 (6.9)	667,665 (62.8)
	06/07	1,120,604	56.5 (11.7)	25.9 (24.9)	35,924 (3.2)	72,602 (6.5)	730,295 (65.2)
	08/09	1,123,509	56.5 (11.6)	27.8 (26.4)	38,033 (3.4)	68,582 (6.1)	747,079 (66.5)
	10/11	1,103,173	56.5 (11.5)	28.6 (27.2)	39,339 (3.6)	63,652 (5.8)	742,856 (67.3)
	12/13	1,046,396	56.7 (11.4)	30.1 (28.4)	39,265 (3.8)	57,731 (5.5)	714,070 (68.2)
	14/15	914,804	57.1 (11.4)	29.2 (28.4)	36,164 (4.0)	49,444 (5.4)	632,296 (69.1)

Graphs corresponding to this table can be found in Supplemental Digital Content 5, http://links.lww.com/MENO/A388. Information on index of multiple deprivation distribution among HT users and nonusers is provided in Supplement Digital Content 4, http://links.lww.com/MENO/A387.
CVD, cardiovascular disease (comprises myocardial infarction, ischemic stroke, and angina pectoris); GP, general practitioner; HT, hormone therapy; SD, standard deviation.

A389) provides additional details of characteristics used to define CVD and CVD risk factors. The distribution of IMD remained stable throughout the study period. HT users were on average less deprived than nonusers; there was a higher proportion of HT users with IMD index 1 to 3 and lower proportion with an IMD index of 4 to 5 (SDC 4, http://links.lww.com/MENO/A387).

Hormone therapy utilization patterns among patients with breast cancer, CVD, and CVD risk factors

The proportions of overall HT use over time among breast cancer patients (4.4%-9.1%) and CVD patients (7.4%-15.3%) was lower than that in the general UK female population (8.7%-20.2%) (SDC 7, http://links.lww.com/MENO/A390). Detailed HT utilization patterns over time in subpopulations

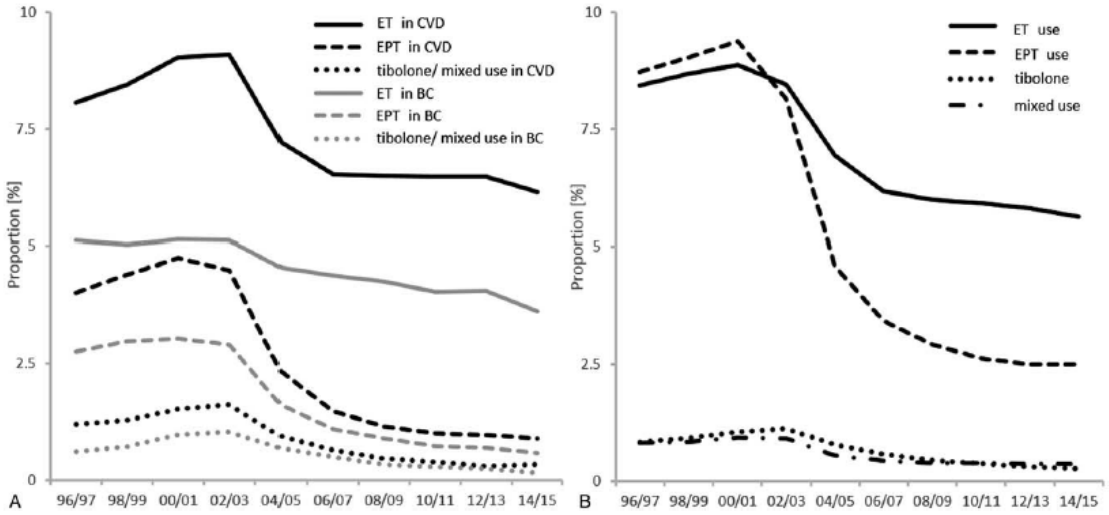

FIG. 2. Proportion of use of different hormone therapy drug types over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Numeric values corresponding to this figure can be found in Supplemental Digital Content 8, http://links.lww.com/MENO/A391. BC, breast cancer; CVD, cardiovascular disease; ET, estrogen therapy; EPT, estrogen plus progestogen therapy.

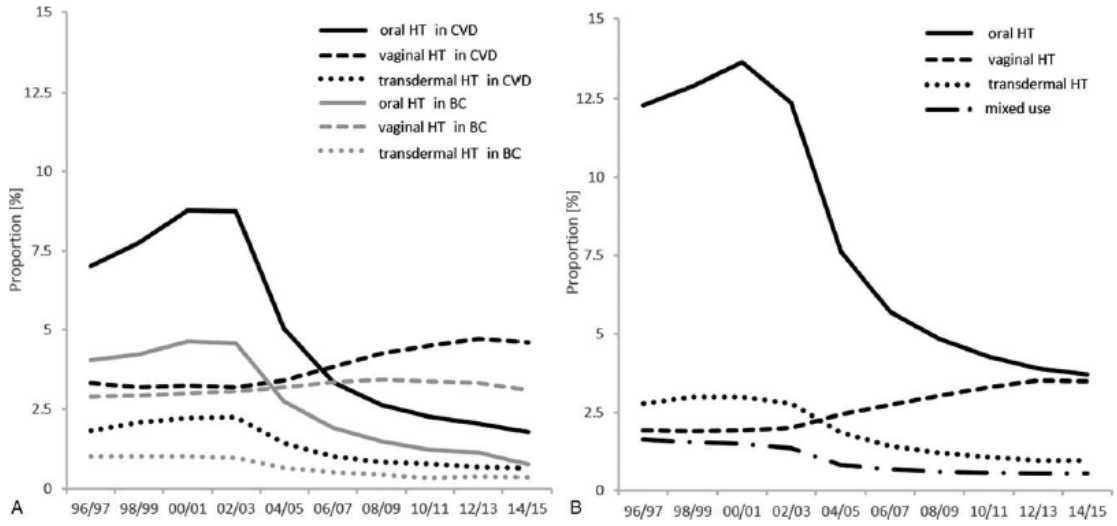

FIG. 3. Proportion of use of different hormone therapy administration routes over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Other hormone therapy/ mixed use is not shown in (**A**) as they were both negligible. Other hormone therapy use includes injections, implants, and nasal administrations. Numeric values corresponding to this figure can be found in Supplemental Digital Content 9, http://links.lww.com/MENO/A392. BC, breast cancer; CVD, cardiovascular disease; HT, hormone therapy.

with breast cancer and CVD revealed that these patients used proportionally more ET (3.6%-5.1% in breast cancer patients, 6.2%-9.1% in CVD patients) than EPT (0.6%-3.0% in breast cancer patients, 0.9%-4.8% in CVD patients) (Fig. 2, SDC 8, http://links.lww.com/MENO/A391). Use of ET in CVD patients was similar to use of ET in the general UK female population with a similar proportion in 2002/2003 (9.1% in CVD patients, 8.4% in the general UK female population) followed by a sharp decrease until 2006/2007 and a subsequent plateau at around 6% in both populations. In contrast, use of ET in breast cancer patients decreased slowly but continuously from 5.1% in 1996/1997 to 3.6% in 2014/2015.

There was a similar pattern of oral HT use over time in breast cancer and CVD patients, but proportionally many fewer HT users (around one-third in breast cancer and one half in CVD patients) compared with the proportion in the general

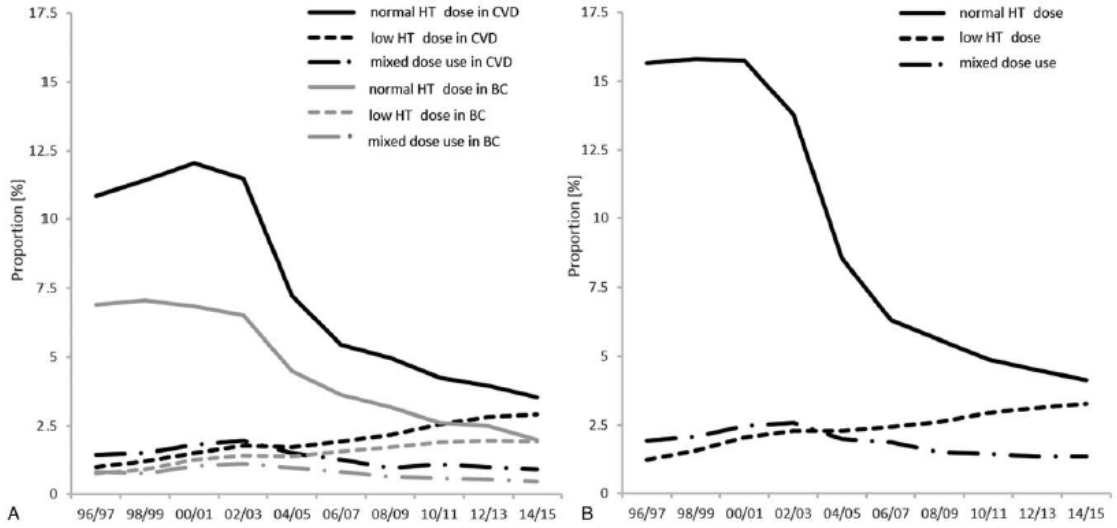

FIG. 4. Proportion of use of different hormone therapy doses over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Numeric values corresponding to this figure can be found in Supplemental Digital Content 10, http://links.lww.com/MENO/A393. BC, breast cancer; CVD, cardiovascular disease; HT, hormone therapy.

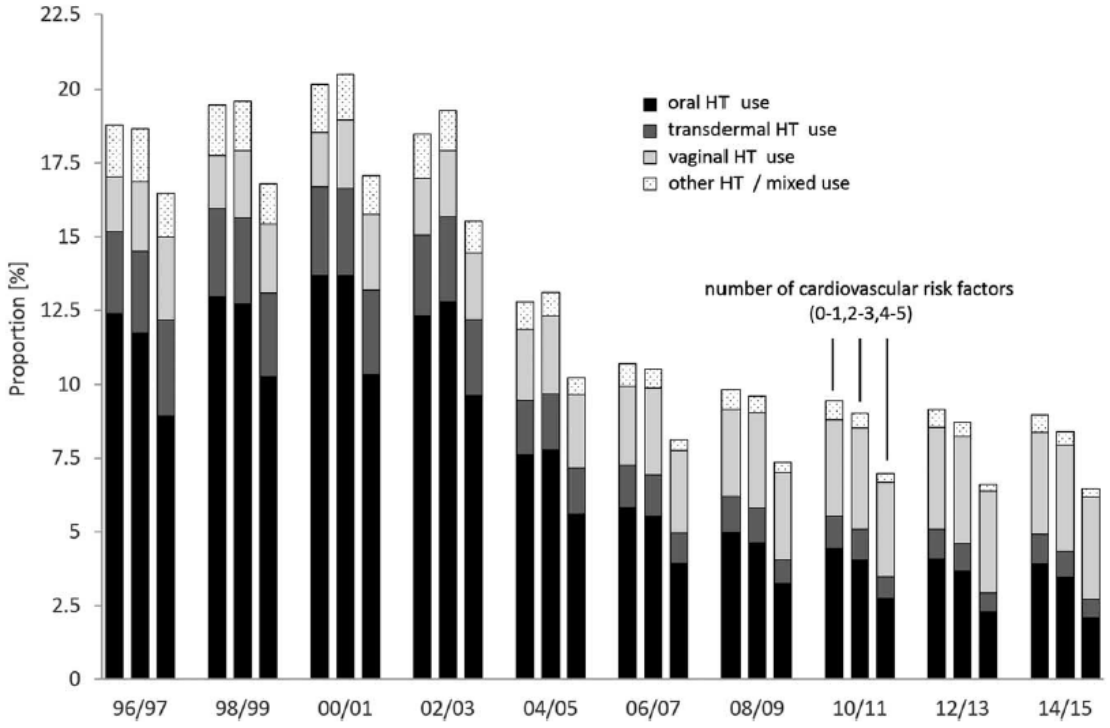

FIG. 5. Proportion of use of different hormone therapy administration routes in a subpopulation with ≥1 cardiovascular risk factor stratified by number of risk factors. Numeric values corresponding to this figure can be found in Supplemental Digital Content 13, http://links.lww.com/MENO/A396. HT, hormone therapy.

UK female population (Fig. 3, SDC 9, http://links.lww.com/MENO/A392). Furthermore, the general UK female population used predominantly oral HT in 2014/2015, closely followed by vaginal HT. In contrast, vaginal HT was used more frequently than oral HT in breast cancer patients starting in 2004/2005 and by CVD patients starting in 2006/2007 (Fig. 3, SDC 9, http://links.lww.com/MENO/A392). Use of different doses of HT was similar among the general UK female population, the breast cancer subpopulation, and the CVD subpopulation with increasing use of lower dose HT over time (Fig. 4, SDC 10, http://links.lww.com/MENO/A393). Concerning mixed use of different HT products within any 2-year block over time, there was more use of mixed HT doses (1.3%-2.6%) than use of mixed drug types (0.4%-0.8%) or administration routes (0.6%-1.6%) (Figs. 2-4, SDC 8-10, http://links.lww.com/MENO/A391-http://links.lww.com/MENO/A393). Combined stratifications of HT drug type, administration route, and dose among breast cancer patients revealed that normal dose vaginal ET steadily decreased over time (1996/1997: 2.3%, 2014/2015: 1.2%), and that low-dose vaginal ET steadily increased over time (1996/1997: 0.4%, 2014/2015: 1.6%), whereas normal-dose oral EPT and ET decreased strongly (EPT: 2.3% in 2002/2003 to 0.3% in 2014/2015, ET: 1.1% in 2002/2003 to 0.1% in 2014/2015) (SDC 11, http://links.lww.com/MENO/A394).

There was slightly more use of HT in the subpopulation of patients with CVD risk factors compared with the general UK female population at the beginning of the study period (1996/1997: 20.1% and 18.8%, respectively). However, the proportion of HT users within the two populations converged in 2014/2015 to 8.7% in both (SDC 7, http://links.lww.com/MENO/A390). Use of different drug types, administration routes, and doses of HT in patients with CVD risk factors were similar to those in the general UK female population throughout the study period (SDC 12, http://links.lww.com/MENO/A395). However, the proportion of HT use in women with 4 to 5 CVD risk factors generally decreased over time (6.5%-17.1%) and had an especially lower prevalence of oral (2.1%-10.3%) and transdermal HT use (0.6%-3.2%), when compared with women with fewer CVD risk factors (Fig. 5, SDC 13, http://links.lww.com/MENO/A396).

DISCUSSION

In this large descriptive study, we quantified the use of HT in the general UK female population, and described patient characteristics of HT users and nonusers between 1996 and 2015. We further described detailed HT utilization patterns among the general UK female population and in subpopulations with breast cancer, CVD, and CVD risk factors over time.

The overall use of HT in this study was consistent with use reported in prior studies conducted in the UK which found a slight increase in HT use from 1996 until 2001, followed by a drop until 2010.[19,20] Our study added previously unreported trends in use of HT between 2011 and 2015, which described a further decline in HT use from 7.9% in 2011 to 7.5% in 2015 in the UK. The continuous decline in the proportion of HT users from 2005 to 2015 was in contrast to the steady increase in proportions of new users of HT during this period (from 0.8% to 1.0%), indicating that duration of HT use likely decreased with time. Before 2006, we observed a 50% decline in new use of HT (from 1.7% in 2001 to 0.8% in 2005). This drop was mainly due to a decrease in new use of HT among patients less than 69 years of age. We observed a 70% decrease in use of EPT, oral HT, and normal-dose HT from 2002/2003 to 2014/2015, potential consequences of the WHI and MWS studies reporting increased CVD and breast cancer risks associated mainly with normal doses of oral EPT.[6,7] The prevalence of ET use also decreased by around 30% in this period, perhaps the result of MWS finding of an increased breast cancer risk associated with any systemic HT (ie, EPT, ET, and tibolone).[7] Furthermore, we observed increased use of vaginal and low dose HT likely as safer options for women with vasomotor symptoms (ie, low-dose HT) and genitourinary symptoms (ie, vaginal HT) requiring HT.[30-32] Use of tibolone and transdermal HT use were negligible possibly for cost reasons. While use of mixed drug types or administration routes was generally negligible early in the study period, by 2014/2015, mixed use of different HT doses was around one third that of low dose HT use and one-fourth that of normal dose use. This may indicate that patients were less likely to change drug types or routes of administration, while they were willing to change HT dose.

The characteristics of HT users changed after 2002/2003. The steep increase in mean age among HT users leveled off at 57 to 58 years, and the mean number of GP contacts increased more among HT users than nonusers potentially because of questioned safety of HT reported in the media. Notably, HT remained a treatment for women of higher socioeconomic status over time.

The prevalence of breast cancer among HT users increased steadily over time, although it was lower throughout the whole study period and its increase less steep than that of nonusers. In 2004, NAMS declared HT contraindicated in women with hormone-sensitive cancer (around 70% of breast cancer diagnoses)[33] and proposed nonhormonal treatment alternatives.[34] In later NAMS position statements,[13,14] this matter was declared as unresolved because study results about risk of progression due to HT use in breast cancer patients were inconclusive.[35,36] Estrogen-depleting treatments of breast cancer such as aromatase inhibitors and tamoxifen were reported to provoke vaginal atrophy and exacerbations of vasomotor symptoms.[37,38] Thus, in women not responding to nonhormonal treatments, low-dose vaginal ET was suggested a safe option to alleviate urogenital atrophy in a literature review.[38] This is a likely reason why we observed slightly decreasing ET use overall, due to decreasing normal-dose oral and vaginal ET use, but strongly increasing low-dose vaginal ET use, while use of normal-dose oral EPT decreased by around 85% from 2002/2003 to 2014/2015 among breast cancer patients.

The previously, increasing prevalence of CVD among HT users decreased after 2002/2003, which coincided with WHI results contesting the claims of cardioprotective effects of HT.[6,39] Considering the convergence of CVD prevalence among HT users and nonusers over time, it seems that the presence of CVD became a less important factor in the decision to prescribe HT. Throughout the whole study period, the proportion of EPT, oral, and normal-dose HT use in CVD patients was around 50% lower, whereas the proportion of vaginal HT use was around 25% higher than that in the general UK female population. This indicates that GPs prescribed HT products resulting in less systemic estrogen exposure for CVD patients. Moreover, we observed that GPs were less likely to prescribe HT with progestogen, perhaps because of the existing evidence suggesting metabolic and vascular effects of progestogen.[40,41]

At the beginning of the study period, the prevalence of CVD risk factors was slightly higher among HT users than nonusers, but converged with time in the two populations. With more than 50% of HT users and nonusers diagnosed with $\geq$1 CVD risk factor, it was not surprising that trends in HT utilization patterns in patients with CVD risk factors were similar to those of the general UK female population. However, HT utilization trends varied according to the number of CVD risk factors. While use of oral and transdermal HT decreased with increasing number of CVD risk factors, use of vaginal HT use was highest in women with $\geq$2 CVD risk factors. It is likely that use of vaginal HT in women with several CVD risk factors was considered a safer choice than systemic HT use.[30-32]

A major strength of this study is its very large patient population of >2 million women, yielding informative results even for subanalyses (eg, detailed HT utilization pattern in breast cancer patients). Additionally, as CPRD prescriptions are issued electronically by the GP, we likely captured near-complete patient prescription records, especially since treatment suggestions from specialists such as gynecologists and endocrinologists, who may treat women at high risk of adverse events, are issued by the GP for reasons of reimbursement. On the contrary, we captured HT prescriptions which we approximated as HT use, though we do not know if women actually filled the prescriptions. This may have resulted in a slight overestimation of HT use. Medication details are provided in the CPRD, which allowed us to describe HT utilization patterns by drug type, administration route, and dose. However, if two different products (eg, vaginal HT and oral HT) were prescribed during the same block, we could not easily determine whether they were used concomitantly or consecutively. In this situation, we categorized them as mixed use, possibly resulting in an overestimation of mixed use and an underestimation of single

HT use. The cross-sectional assessment of prescriptions and diagnoses further means that the time of diagnoses and prescriptions remained unknown in this study. HT had to be currently prescribed during a certain block, whereas for chronic disease diagnoses, we did not differentiate between diagnoses made during or before a block. A block was 2 years long, whereas the average observation period for HT users was around 18 years. This means that diagnoses were more likely made before a block than within a block. Last, even though we required women to have 3 years of history in the database to capture incident HT use, women may not have been true first-time HT users if they changed GP practices and had longer gaps between periods of HT use. Therefore, we may have slightly overestimated the number of new HT users.

Despite these limitations, this is, to our knowledge, the first study to describe in detail the long-term impact of guideline changes on safe HT use in 2003/2004. The study focused on time trends of HT use in the general UK female population, on patient characteristics of HT users and nonusers, and on detailed HT utilization patterns in the general UK female population, and also in subpopulations with breast cancer, CVD, and CVD risk factors.

CONCLUSIONS

This large descriptive study provides information on the use of HT in the UK following efforts of the international menopause societies to promote safe HT use after publications of the WHI and MWS results. Our study suggests that guideline changes implemented in UK clinical practice guided doctors and women towards safer HT use with shorter durations, less systemic exposure (vaginal formulations, lower doses of HT), and ET rather than EPT prescriptions, particularly among women with pre-existing CVD or breast cancer.

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Supplementary File 1. Detailed information on categorization of hormone therapy product's estrogen dose strength

Low dose (including ultra-low dose): ≤1 mg estradiol oral,[1] ≤0.45 mg conjugated estrogen oral,[1,2] ≤37.5 µg estradiol transdermal,[1,2] ≤50 µg estradiol vaginal,[3] ≤0.3 mg conjugated estrogens/≤0.5 g vaginal cream[3]

Normal dose: all other than above mentioned ultra-low and low dose estrogen applications, injections, implants,[4] and nasal applications

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Supplementary File2. Numeric values corresponding to Figure1 of the main manuscript. Proportion of overall and new hormone therapy use in the general UK female population from 1996 to 2015

Supplementary Table1. Annual proportion of overall and new hormone therapy use in women aged 40-79 years from 1996 to 2015

Year	Number of women with ≥1 HT prescription	Number of women with a first HT prescription	Number of eligible women (denominator)	Proportion of overall HT use [%] (95% CI)	Proportion of new HT use [%] (95% CI)
1996	142,712	17,349	866,426	16.5 (16.4-16.6)	2.00 (1.97-2.03)
1997	156,954	16,378	920,447	17.1 (17.0-17.1)	1.78 (1.75-1.81)

1998	166,618	15,920	961,153	17.4 (17.3-17.4)	1.66 (1.63-1.68)
1999	176,238	16,674	997,337	17.7 (17.6-17.7)	1.67 (1.65-1.70)
2000	189,535	17,994	1,030,248	18.4 (18.3-18.5)	1.75 (1.72-1.77)
2001	197,061	17,559	1,061,319	18.6 (18.5-18.6)	1.65 (1.63-1.68)
2002	197,017	15,094	1,090,053	18.1 (18.0-18.1)	1.38 (1.36-1.41)
2003	168,813	10,881	1,111,530	15.2 (15.1-15.3)	0.98 (0.96-1.00)
2004	135,698	10,740	1,135,903	11.9 (11.9-12.0)	0.95 (0.93-0.96)
2005	119,158	9536	1,153,660	10.3 (10.3-10.4)	0.83 (0.81-0.84)
2006	110,535	10,056	1,170,919	9.4 (9.4-9.5)	0.86 (0.84-0.88)
2007	105,387	10,377	1,178,555	8.9 (8.9-9.0)	0.88 (0.86-0.90)
2008	100,254	10,728	1,173,476	8.5 (8.5-8.6)	0.91 (0.90-0.93)
2009	96,596	10,817	1,168,740	8.3 (8.2-8.3)	0.93 (0.91-0.94)
2010	92,779	11,135	1,149,867	8.1 (8.0-8.1)	0.97 (0.95-0.99)
2011	88,258	11,123	1,122,420	7.9 (7.8-7.9)	0.99 (0.98-1.01)
2012	84,319	10,992	1,091,857	7.7 (7.7-7.8)	1.01 (0.99-1.03)
2013	80,194	10,465	1,051,561	7.6 (7.6-7.7)	1.00 (0.98-1.01)
2014	73,767	9893	961,973	7.7 (7.6-7.7)	1.03 (1.01-1.05)
2015	61,948	8335	821,080	7.5 (7.5-7.6)	1.02 (0.99-1.04)

HT: hormone therapy, CI: confidence interval

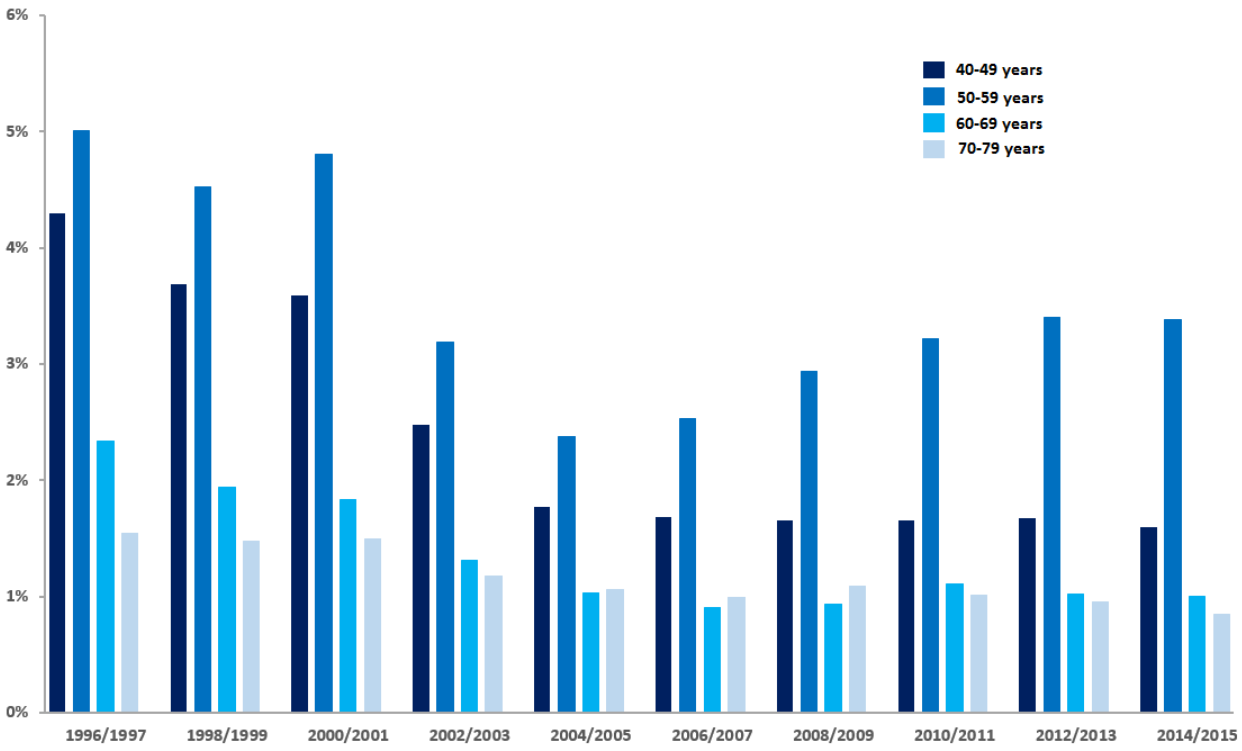
Supplementary File3. Proportion of new hormone therapy use in the general UK female population within 2-year blocks stratified by age groups

Supplementary Table2. Proportion of new hormone therapy use in women aged 40-79 years in 2-year blocks stratified by age groups

Years	Age group [years]	Number of women with a first HT prescription	Number of eligible women (denominator)	Proportion of new HT use [%] (95% CI)
1996/1997	40-49	13633	317,311	4.30 (4.23-4.38)
	50-59	12363	246,725	5.01 (4.93-5.10)
	60-69	4846	207,305	2.34 (2.27-2.40)
	70-79	2885	187,456	1.54 (1.48-1.60)
1998/1999	40-49	12482	338,418	3.69 (3.63-3.75)
	50-59	12803	282,693	4.53 (4.45-4.61)
	60-69	4301	221,352	1.94 (1.89-2.00)
	70-79	3008	203,331	1.48 (1.43-1.53)
2000/2001	40-49	13254	369,282	3.59 (3.53-3.65)
	50-59	14948	310,893	4.81 (4.73-4.88)
	60-69	4261	231,940	1.84 (1.78-1.89)
	70-79	3090	207,381	1.49 (1.44-1.54)
2002/2003	40-49	9888	399,048	2.48 (2.43-2.53)
	50-59	10487	329,125	3.19 (3.13-3.25)
	60-69	3168	241,123	1.31 (1.27-1.36)
	70-79	2432	206,566	1.17 (1.13-1.22)
2004/2005	40-49	7514	424,528	1.77 (1.73-1.81)
	50-59	7955	335,495	2.37 (2.32-2.42)
	60-69	2632	254,903	1.03 (0.99-1.07)
	70-79	2175	204,582	1.06 (1.02-1.11)
2006/2007	40-49	7454	442,125	1.69 (1.65-1.72)
	50-59	8497	336,421	2.53 (2.47-2.58)
	60-69	2442	269,653	0.91 (0.87-0.94)

	70-79	2040	205,029	1.00 (0.95-1.04)
2008/2009	40-49	7265	439,834	1.65 (1.61-1.69)
	50-59	9481	323,052	2.93 (2.88-2.99)
	60-69	2619	280,409	0.93 (0.90-0.97)
	70-79	2180	200,948	1.08 (1.04-1.13)
2010/2011	40-49	7010	424,954	1.65 (1.61-1.69)
	50-59	10186	316,770	3.22 (3.15-3.28)
	60-69	3113	280,325	1.11 (1.07-1.15)
	70-79	1949	193,760	1.01 (0.96-1.05)
2012/2013	40-49	6537	391,104	1.67 (1.63-1.71)
	50-59	10434	306,591	3.40 (3.34-3.47)
	60-69	2734	268,016	1.02 (0.98-1.06)
	70-79	1752	183,506	0.95 (0.91-1.00)
2014/2015	40-49	5120	321,621	1.59 (1.55-1.64)
	50-59	9334	275,982	3.38 (3.32-2.45)
	60-69	2343	234,920	1.00 (0.96-1.04)
	70-79	1431	169,694	0.84 (0.80-0.89)

HT: hormone therapy, CI: confidence interval



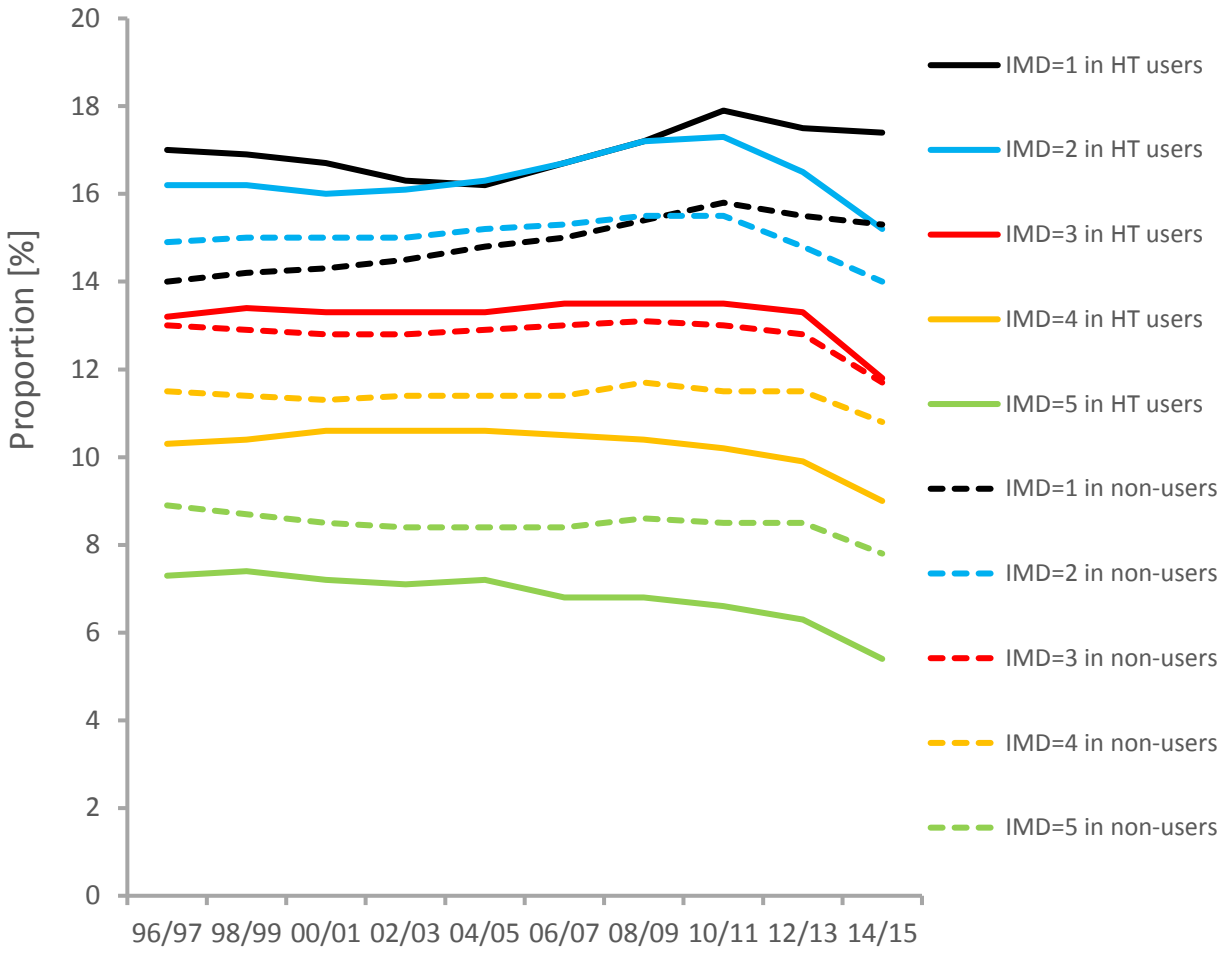
Supplementary Figure1. Proportion of new hormone therapy use in women aged 40-79 years in 2-year blocks stratified by age groups

Supplementary File 4. Index of multiple deprivation of hormone therapy users and non-users in quintiles from 1996/1997 to 2014/2015

Supplementary Table3. Proportion of index of multiple deprivation (IMD) of hormone therapy users and non-users in quintiles over time where IMD=1 equals "least deprived" and IMD=5 equals "most deprived"

Years	Exposure status	Number of women with IMD=1 (%)	Number of women with IMD=2 (%)	Number of women with IMD=3 (%)	Number of women with IMD=4 (%)	Number of women with IMD=5 (%)	Number of women with missing information on IMD (%)
1996/ 1997	**HT users**	30,535 (17.0)	29,126 (16.2)	23,807 (13.2)	18,557 (10.3)	13,193 (7.3)	64,816 (36.0)
	Non-users	109,201 (14.0)	116,281 (14.9)	101,181 (13.0)	89,163 (11.5)	69,092 (8.9)	293,845 (37.7)
1998/ 1999	**HT users**	34,328 (16.9)	32,978 (16.2)	27,238 (13.4)	21,122 (10.4)	14,971 (7.4)	72,822 (35.8)
	Non-users	119,223 (14.2)	126,592 (15.0)	108,946 (12.9)	96,153 (11.4)	73.099 (8.7)	318,322 (37.8)
2000/ 2001	**HT users**	37,677 (16.7)	36,205 (16.0)	30,177 (13.3)	23,899 (10.6)	16,186 (7.2)	82,032 (36.3)
	Non-users	127,601 (14.3)	133,919 (15.0)	113,860 (12.8)	101,157 (11.3)	75,664 (8.5)	341,119 (38.2)
2002/ 2003	**HT users**	35,646 (16.3)	35,264 (16.1)	29,053 (13.3)	23,200 (10.6)	15,474 (7.1)	80,245 (36.7)
	Non-users	138,434 (14.5)	143,311 (15.0)	122,233 (12.8)	108,876 (11.4)	80,368 (8.4)	363,758 (38.0)
2004/ 2005	**HT users**	25,343 (16.2)	25,492 (16.3)	20,806 (13.3)	16,517 (10.6)	11,192 (7.2)	56,963 (36.4)
	Non-users	156,999 (14.8)	161,155 (15.2)	137,139 (12.9)	121,454 (11.4)	88,727 (8.4)	397,630 (37.4)
2006/ 2007	**HT users**	22,135 (16.7)	22,164 (16.7)	17,946 (13.5)	13,914 (10.5)	9039 (6.8)	47,426 (35.8)
	Non-users	167,970 (15.0)	171,561 (15.3)	145,437 (13.0)	128,139 (11.4)	93,847 (8.4)	413,650 (36.9)
2008/ 2009	**HT users**	20,719 (17.2)	20,757 (17.2)	16,294 (13.5)	12,549 (10.4)	8159 (6.8)	42,256 (35.0)
	Non-users	172,410 (15.4)	173,733 (15.5)	146,961 (13.1)	130,838 (11.7)	96,526 (8.6)	403,041 (35.9)
2010/ 2011	**HT users**	20,185 (17.9)	19,495 (17.3)	15,197 (13.5)	11,435 (10.2)	7392 (6.6)	389,932 (34.6)
	Non-users	174,372 (15.8)	170,780 (15.5)	143,214 (13.0)	127,124 (11.5)	94,081 (8.5)	393,602 (35.7)
2012/ 2013	**HT users**	18,008 (17.5)	17,004 (16.5)	13,623 (13.3)	10,144 (9.9)	6497 (6.3)	37,545 (36.5)
	Non-users	162,427 (15.5)	155,261 (14.8)	134,053 (12.8)	120,324 (11.5)	88,633 (8.5)	385,698 (36.9)
2014/ 2015	**HT users**	15,167 (17.4)	13,263 (15.2)	10,314 (11.8)	7889 (9.0)	4733 (5.4)	36,047 (41.2)
	Non-users	139,685 (15.3)	127,573 (14.0)	106,929 (11.7)	98,653 (10.8)	71,467 (7.8)	370,497 (40.5)

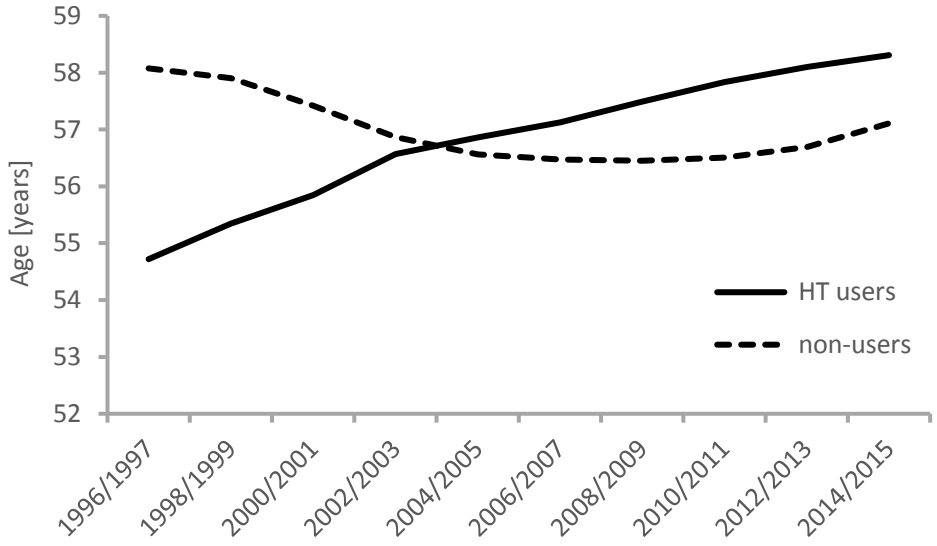
IMD: index of multiple deprivation, HT: hormone therapy



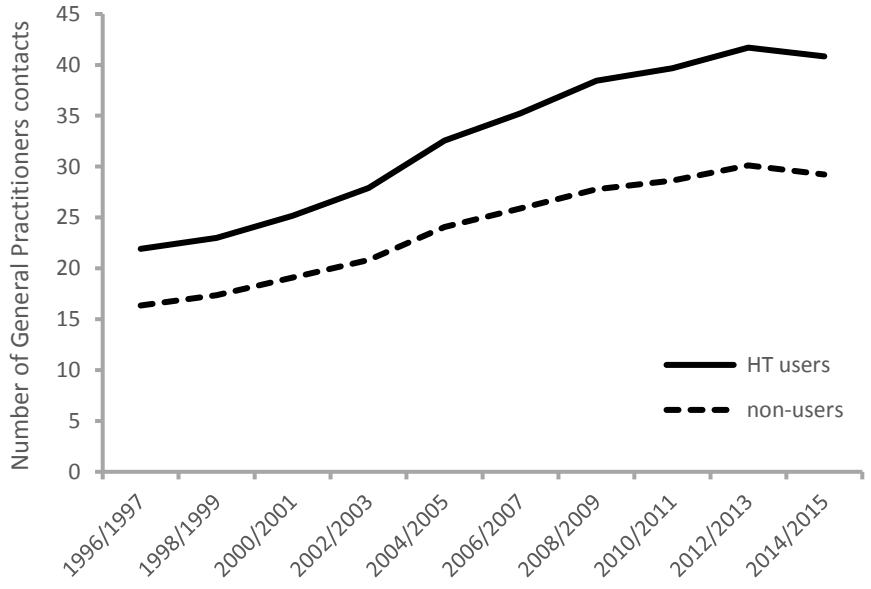
Supplementary Figure2. Prevalence of index of multiple deprivation (IMD) of hormone therapy users and non-users in fifths over time where IMD=1 equals "least deprived" and IMD=5 equals "most deprived"

IMD: index of multiple deprivation, HT: hormone therapy

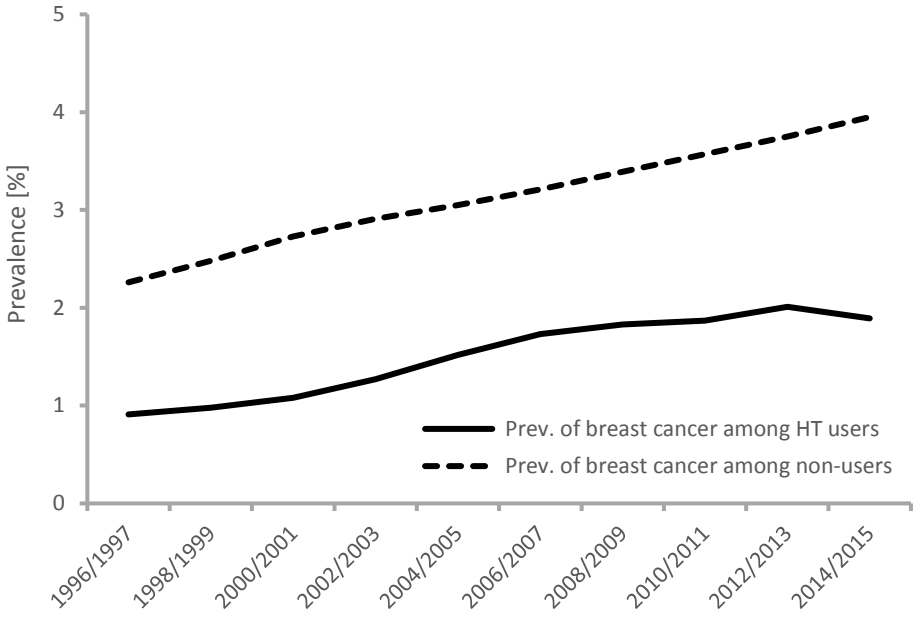
Supplementary File5. Graphs corresponding to Table1 of the main manuscript. Main patient characteristics of hormone therapy users and non-users from 1996/1997 to 2014/2015



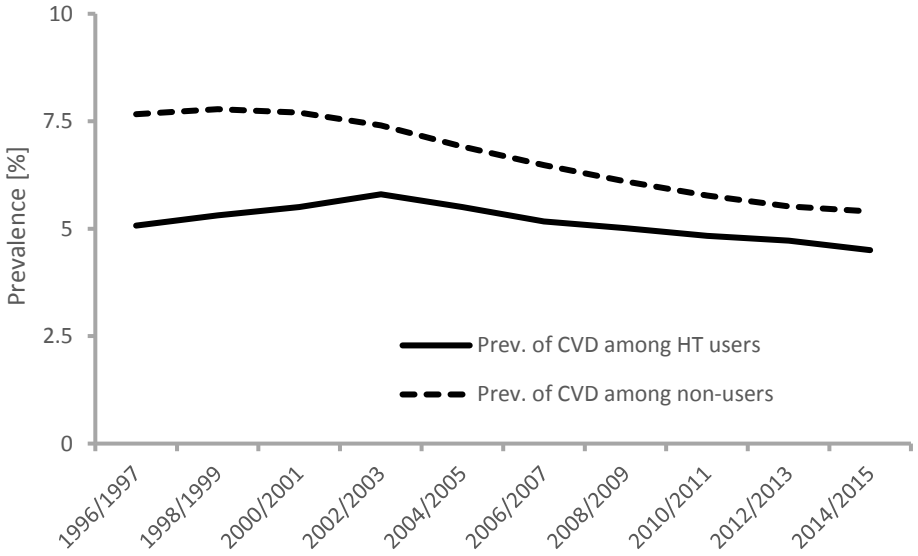
Supplementary Figure3. Mean age among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
HT: hormone therapy



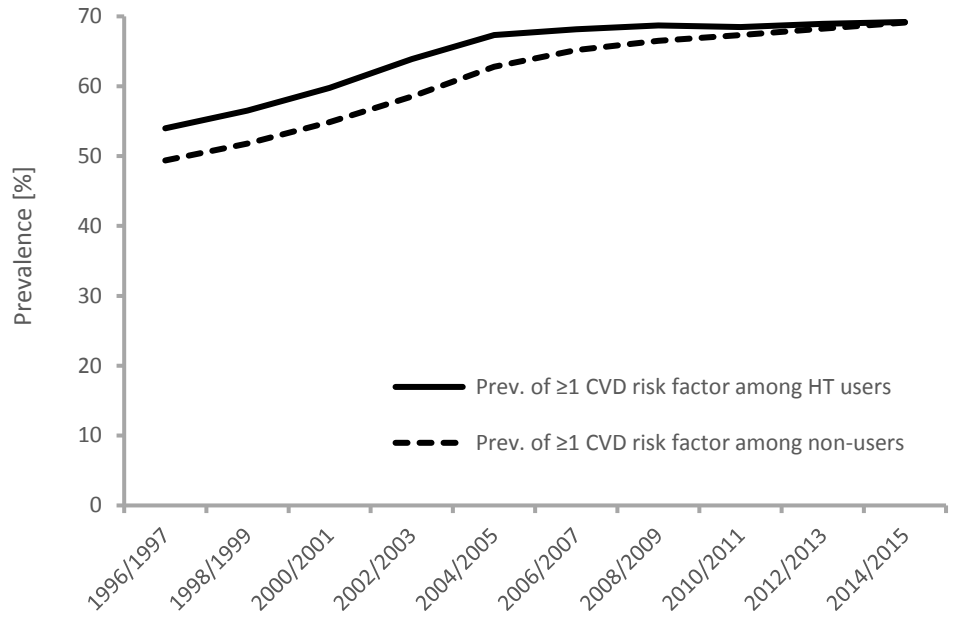
Supplementary Figure4. Mean number of general practitioners contacts among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
HT: hormone therapy



Supplementary Figure5. Prevalence of breast cancer among hormone therapy users and in the general UK female population from 1996/1997 to 2014/2015
HT: hormone therapy



Supplementary Figure6. Prevalence of cardiovascular disease among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
CVD: cardiovascular disease, HT: hormone therapy



Supplementary Figure7. Prevalence of ≥1 cardiovascular risk factor among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015

Prev.: prevalence, CVD: cardiovascular disease, HT: hormone therapy

Supplementary File6. Descriptive analytics of characteristics comprised in the definition of cardiovascular disease and cardiovascular risk factors of hormone therapy users and non-users from 1996/1997 to 2014/2015

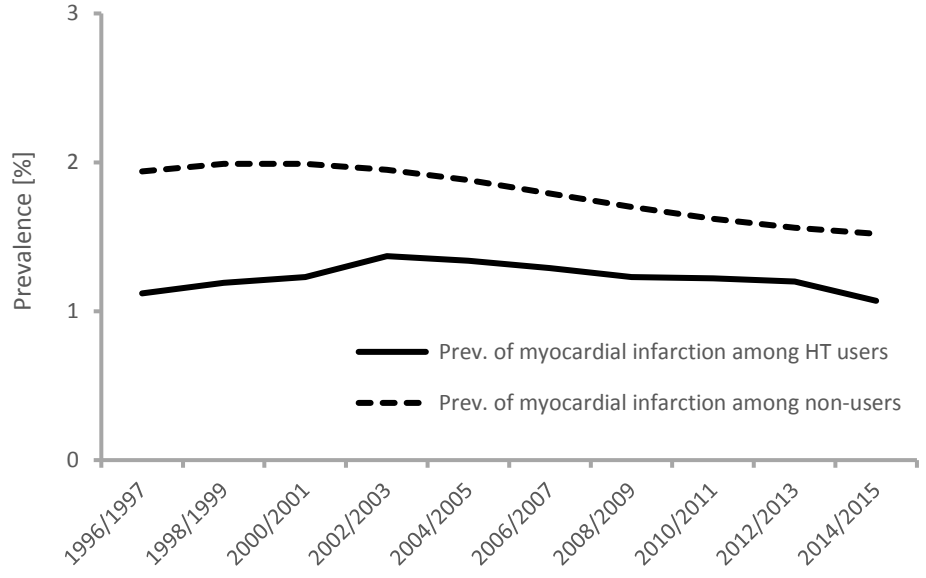
Supplementary Table4. Descriptive analytics of characteristics comprised in the definition of cardiovascular disease and cardiovascular risk factors of hormone therapy users and non-users from 1996/1997 to 2014/2015

Exp. Stat.	Years	No. of women	MI (%)	Isch. stroke (%)	AP (%)	Curr. Smok. (%)	Obesity[a] (%)	Hypertens. (%)	Hyperlip. (%)	Diab. (%)
HT users	96/97	180,034	2014 (1.1)	2466 (1.4)	6347 (3.5)	40,690 (22.6)	26,358 (14.6)	29,144 (16.2)	9285 (5.2)	3798 (2.1)
	98/99	203,459	2420 (1.2)	3092 (1.5)	7375 (3.6)	47,022 (23.1)	31,606 (15.5)	36,683 (18.0)	11,360 (5.6)	4964 (2.4)
	00/01	226,176	2788 (1.2)	3850 (1.7)	8290 (3.7)	52,162 (23.1)	37,662 (16.7)	46,291 (20.5)	14,122 (6.2)	6630 (2.9)
	02/03	218,882	3003 (1.4)	4068 (1.9)	8279 (3.8)	49,305 (22.5)	39,712 (18.1)	51,524 (23.5)	17,223 (7.9)	7726 (3.5)
	04/05	156,313	2095 (1.3)	2868 (1.8)	5382 (3.4)	33,655 (21.5)	30,088 (19.3)	39,327 (25.2)	15,714 (10.1)	6207 (4.0)
	06/07	132,624	1711 (1.3)	2421 (1.8)	4117 (3.1)	25,432 (19.2)	27,305 (20.6)	33,657 (25.4)	15,727 (11.8)	5671 (4.3)
	08/09	120,734	1480 (1.2)	2336 (1.9)	3402 (2.8)	21,834 (18.1)	26,651 (22.1)	30,926 (25.6)	16,213 (13.4)	5510 (4.6)
	10/11	112,636	1377 (1.2)	2240 (2.0)	2833 (2.5)	18,985 (16.9)	25,730 (22.8)	28,522 (25.3)	16,013 (14.2)	5541 (4.9)

	12/13	102,821	1232 (1.2)	2188 (2.1)	2269 (2.2)	15,684 (15.3)	24,086 (23.4)	26,356 (25.6)	15,701 (15.3)	5377 (5.2)
	14/15	87,413	931 (1.1)	1859 (2.1)	1777 (2.0)	12,083 (13.8)	21,286 (24.4)	22,165 (25.4)	13,765 (15.8)	4878 (5.6)
Non-users	96/97	778,763	15,104 (2.0)	21,337 (2.7)	35,48 2 (4.6)	139,110 (17.9)	112,697 (14.5)	146,515 (18.8)	32,603 (4.2)	30,047 (3.9)
	98/99	842,335	16,748 (2.0)	24,255 (2.9)	38,56 7 (4.6)	155,7761 (18.5)	132,249 (15.7)	167,330 (19.9)	41,706 (5.0)	35,718 (4.2)
	00/01	893,320	17,772 (2.0)	25,930 (2.9)	40,54 8 (4.5)	170,385 (19.1)	154,328 (17.3)	191,346 (21.4)	53,438 (6.0)	42,778 (4.8)
	02/03	956,980	18,621 (2.0)	27,374 (2.9)	41,28 8 (4.3)	185,352 (19.4)	185,253 (19.4)	220,926 (23.1)	71,060 (7.4)	51,594 (5.4)
	04/05	1,063,195	19,959 (1.9)	29,493 (2.8)	41,10 5 (3.9)	203,615 (19.2)	228,243 (21.5)	266,930 (25.1)	102,465 (9.6)	62,521 (5.9)
	06/07	1,120,604	20,081 (1.8)	30,067 (2.7)	38,72 1 (3.5)	207,450 (18.5)	268,916 (24.0)	290,455 (25.9)	125,602 (11.2)	70,511 (6.3)
	08/09	1,123,509	19,136 (1.7)	29,613 (2.6)	34,48 2 (3.1)	205,485 (18.3)	289,924 (25.8)	294,113 (26.2)	138,096 (12.2)	75,350 (6.7)
	10/11	1,103,173	17,842 (1.6)	28,964 (2.6)	29,70 6 (2.7)	198,000 (18.0)	299,893 (27.2)	288,028 (26.1)	144,054 (13.1)	78,058 (7.1)
	12/13	1,046,396	16,278 (1.6)	27,574 (2.6)	25,08 9 (2.4)	178,119 (17.0)	294,418 (28.1)	275,668 (26.3)	146,115 (14.0)	78,523 (7.5)
	14/15	914,804	13,879 (1.5)	24,582 (2.7)	20,06 0 (2.2)	146,214 (16.0)	266,759 (26.2)	243,424 (26.6)	135,732 (14.8)	71,742 (7.8)

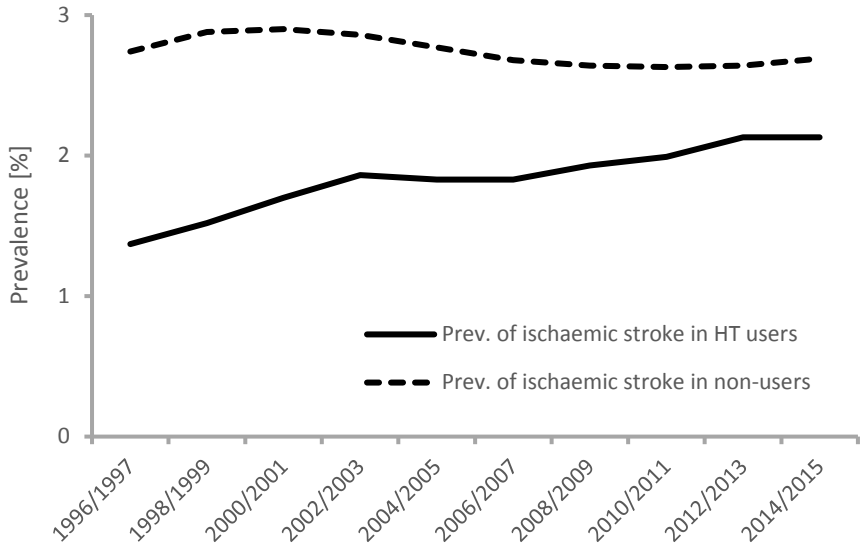
Exp.: exposure, Stat. : status, HT: hormone therapy, No. : number, MI: myocardial infarction, Isch.: ischemic, AP: angina pectoris, Curr.: current, smok.: smoking, hypertens.: hypertension, hyperlip.: hyperlipidemia, diab.: diabetes

[a] Obesity was defined as BMI >30 kg/m^2 or a Read Code for obesity

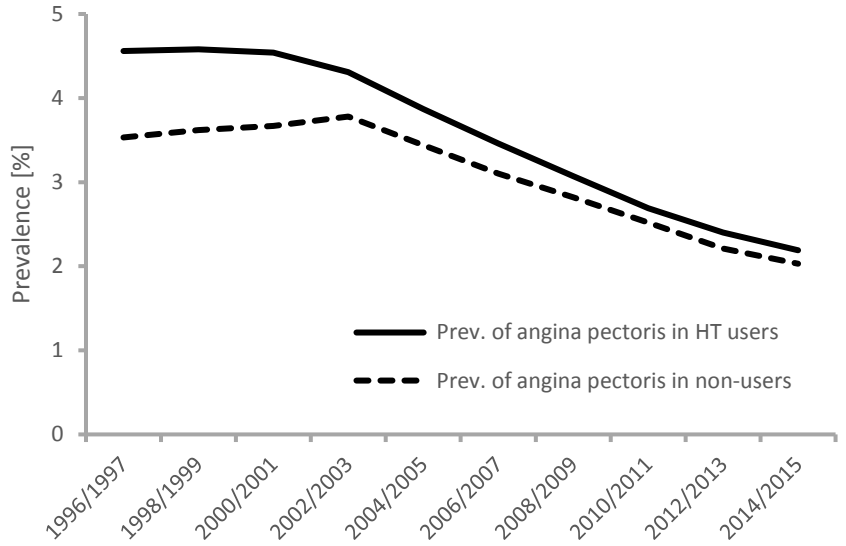


Supplementary Figure8. Prevalence of myocardial infarction among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015

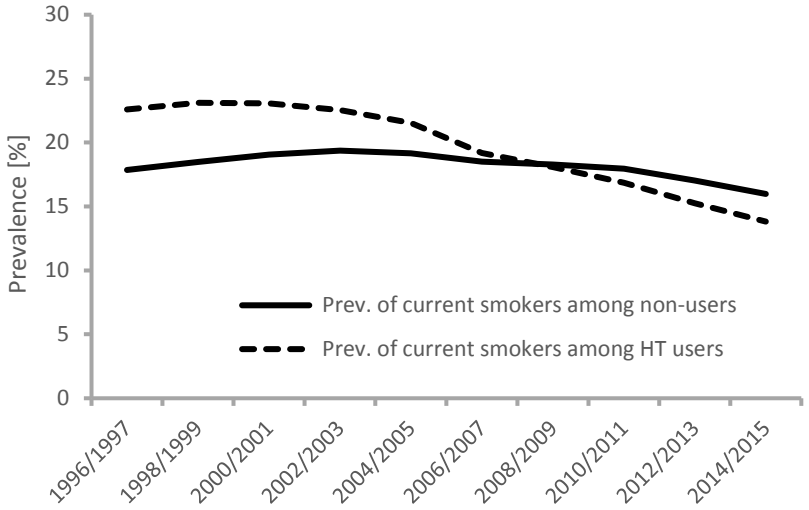
Prev.: prevalence, HT: hormone therapy



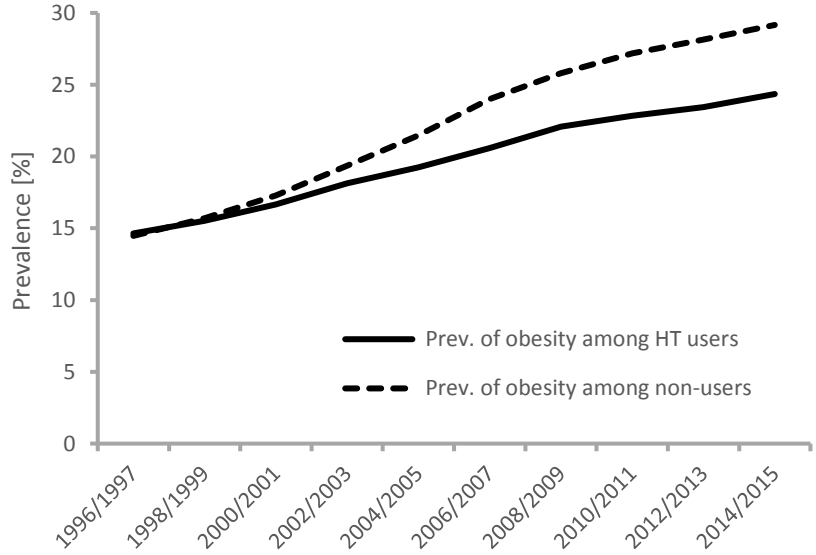
Supplementary Figure9. Prevalence of ischaemic stroke among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



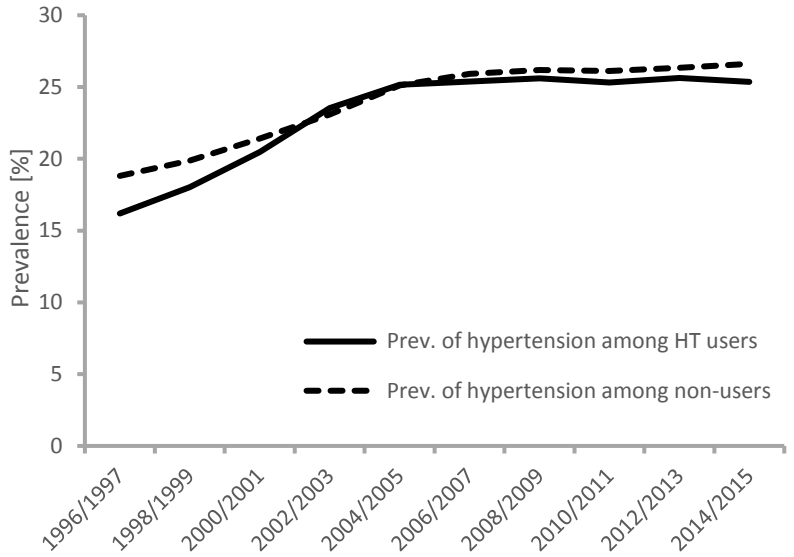
Supplementary Figure10. Prevalence of angina pectoris among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



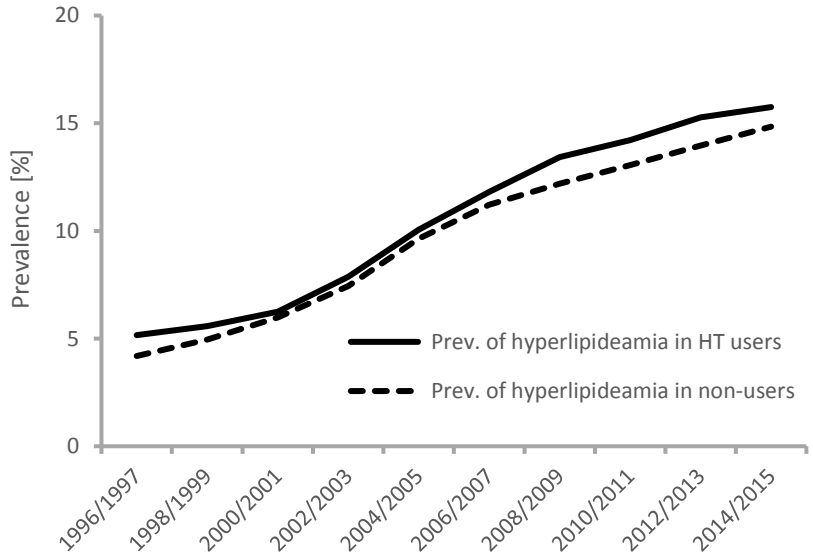
Supplementary Figure11. Prevalence of current smokers among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



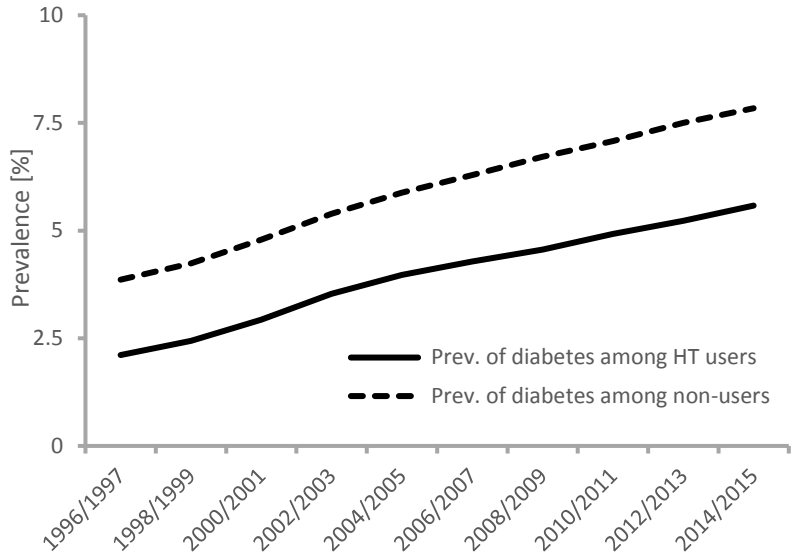
Supplementary Figure12. Prevalence of obesity among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



Supplementary Figure13. Prevalence of hypertension among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



Supplementary Figure14. Prevalence of hyperlipidemia among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy



Supplementary Figure15. Prevalence of diabetes among hormone therapy users and non-users in the general UK female population from 1996/1997 to 2014/2015
Prev.: prevalence, HT: hormone therapy

Supplementary File7. Hormone therapy use in the general UK female population and sub-populations with breast cancer, cardiovascular disease, and cardiovascular disease risk factors

Supplementary Table5. Hormone therapy use in UK general practice and sub-populations with breast cancer, cardiovascular disease, and cardiovascular risk factors

Years	HT users in the general UK female population (%)	HT users in the breast cancer population (%)	HT users in the CVD population (%)	HT users in the population with ≥1 cardiovascular risk factors (%)
1996/1997	180,034 (18.8)	1633 (8.5)	9130 (13.3)	97,189 (20.2)
1998/1999	203,459 (19.5)	1999 (8.7)	10,799 (14.1)	114,983 (20.9)
2000/2001	226,176 (20.2)	2449 (9.1)	12,449 (15.3)	135,204 (21.6)
2002/2003	218,882 (18.6)	2780 (9.1)	12,693 (15.2)	139,837 (20.0)
2004/2005	156,313 (12.8)	2380 (6.8)	8591 (10.5)	105,207 (13.6)
2006/2007	132,624 (10.6)	2289 (6.0)	6862 (8.6)	90,398 (11.0)
2008/2009	120,734 (9.7)	2214 (5.5)	6050 (8.1)	82,955 (10.0)
2010/2011	112,636 (9.3)	2102 (5.1)	5441 (7.9)	77,106 (9.4)
2012/2013	102,821 (8.9)	2066 (5.0)	4852 (7.8)	70,899 (9.0)
2014/2015	87,413 (8.7)	1651 (4.4)	3993 (7.4)	60,487 (8.7)

HT: hormone therapy, CVD: cardiovascular disease

Supplementary File8. Numeric values corresponding to Figure2 of the main manuscript. Proportion of use of different hormone therapy drug types over time in A) the cardiovascular disease and breast cancer sub-populations and B) the general UK female population

Supplementary Table6. Hormone therapy use in the general UK female population stratified by drug type from 1996/1997 to 2014/2015

Years	Number of ET users (%)	Number of EPT users (%)	Number of tibolone users (%)	Number of mixed users (%)
1996/1997	80,813 (8.4)	83,477 (8.7)	7857 (0.8)	7887 (0.8)
1998/1999	90,758 (8.7)	94,338 (9.0)	9536 (0.9)	8827 (0.8)
2000/2001	99,181 (8.9)	104,990 (9.4)	11,709 (1.1)	10,296 (0.9)
2002/2003	99,269 (8.4)	95,701 (8.1)	13,166 (1.1)	10,746 (0.9)
2004/2005	84,353 (6.9)	55,999 (4.6)	9434 (0.8)	6527 (0.5)
2006/2007	77,315 (6.2)	42,908 (3.4)	6970 (0.6)	5431 (0.4)
2008/2009	74,362 (6.0)	36,210 (2.9)	5482 (0.4)	4680 (0.4)
2010/2011	71,780 (5.9)	31,979 (2.6)	4354 (0.4)	4523 (0.4)
2012/2013	66,575 (5.8)	28,688 (2.5)	3482 (0.3)	4076 (0.4)
2014/2015	56,290 (5.6)	25,015 (2.5)	2640 (0.3)	3468 (0.4)

ET: estrogen therapy, EPT: estrogen plus progestogen therapy

Supplementary Table7. Hormone therapy use in cardiovascular disease patients stratified by drug type from 1996/1997 to 2014/2015

Years	Number of ET users (%)	Number of EPT users (%)	Number of tibolone or mixed users (%)
1996/1997	5541 (8.1)	2765 (4.0)	824 (1.2)
1998/1999	6455 (8.5)	3359 (4.4)	985 (1.3)
2000/2001	7342 (9.0)	3869 (4.8)	1238 (1.5)
2002/2003	7585 (9.1)	3758 (4.5)	1350 (1.6)
2004/2005	5913 (7.2)	1907 (2.3)	771 (0.9)
2006/2007	5178 (6.5)	1175 (1.5)	509 (0.6)
2008/2009	4847 (6.5)	856 (1.2)	347 (0.5)
2010/2011	4474 (6.5)	695 (1.0)	272 (0.4)
2012/2013	4055 (6.5)	603 (1.0)	194 (0.3)
2014/2015	3285 (6.2)	474 (0.9)	174 (0.3)

ET: estrogen therapy, EPT: estrogen plus progestogen therapy

Supplementary Table8. Hormone therapy use in breast cancer patients stratified by drug type from 1996/1997 to 2014/2015

Years	Number of ET users (%)	Number of EPT users (%)	Number of tibolone or mixed users (%)
1996/1997	984 (5.1)	531 (2.8)	118 (0.6)
1998/1999	1153 (5.0)	682 (3.0)	164 (0.7)
2000/2001	1378 (5.1)	812 (3.0)	259 (1.0)
2002/2003	1570 (5.1)	894 (2.9)	316 (1.0)
2004/2005	1583 (4.6)	556 (1.6)	241 (0.7)
2006/2007	1677 (4.4)	422 (1.1)	190 (0.5)
2008/2009	1713 (4.3)	364 (0.9)	137 (0.3)
2010/2011	1673 (4.0)	308 (0.7)	121 (0.3)
2012/2013	1676 (4.1)	290 (0.7)	100 (0.2)
2014/2015	1370 (3.6)	220 (0.6)	61 (0.2)

ET: estrogen therapy, EPT: estrogen plus progestogen therapy

Supplementary File9. Numeric values corresponding to Figure3 of the main manuscript. Proportion of use of different hormone therapy administration routes over time in A) the cardiovascular disease breast cancer sub-populations and B) the general UK female population

Supplementary Table9. Hormone therapy use in the general UK female population stratified by administration route from 1996/1997 to 2014/2015

Years	Number of oral HT users (%)	Number of vaginal HT users (%)	Number of transdermal HT users (%)	Number of other[a] HT users (%)	Number of mixed users (%)
1996/1997	117,698 (12.3)	18,536 (1.9)	26,779 (2.8)	1397 (0.2)	15,624 (1.6)
1998/1999	134,890 (12.9)	19,735 (1.9)	31,122 (3.0)	1586 (0.2)	16,126 (1.5)
2000/2001	152,759 (13.7)	21,693 (1.9)	33,557 (3.0)	1447 (0.1)	16,720 (1.5)
2002/2003	145,467 (12.4)	23,485 (2.0)	32,620 (2.8)	1379 (0.1)	15,931 (1.4)
2004/2005	92,859 (7.6)	29,905 (2.5)	22,675 (1.9)	930 (0.1)	9944 (0.8)
2006/2007	71,523 (5.7)	34,227 (2.7)	17,840 (1.4)	550 (0.0)	8484 (0.8)
2008/2009	60,172 (4.8)	37,718 (3.0)	14,928 (1.2)	353 (0.0)	7563 (0.6)
2010/2011	51,894 (4.3)	40,296 (3.3)	13,113 (1.1)	145 (0.0)	7188 (0.6)
2012/2013	44,880 (3.9)	40,293 (3.5)	11,209 (1.0)	N/A[b]	6435 (0.6)
2014/2015	37,242 (3.7)	34,998 (3.5)	9680 (1.0)	N/A[b]	5492 (0.6)

HT: hormone therapy

[a] other hormone therapy use includes injections, implants, and nasal administrations

[b] N/A: not applicable as cell counts <5 are not reportable due to Medicines and Healthcare products Regulatory Agency (MHRA) regulations

Supplementary Table10. Hormone therapy use in cardiovascular disease patients stratified by administration route from 1996/1997 to 2014/2015

Years	Number of oral HT users (%)	Number of vaginal HT users (%)	Number of transdermal HT users (%)	Number of other[a] HT or mixed users (%)
1996/1997	4820 (7.0)	2287 (3.3)	1262 (1.8)	761 (1.1)
1998/1999	5930 (7.8)	2447 (3.2)	1591 (2.1)	831 (1.1)
2000/2001	7135 (8.8)	2648 (3.3)	1813 (2.2)	853 (1.1)
2002/2003	7314 (8.8)	2674 (3.2)	1869 (2.2)	836 (1.0)
2004/2005	4148 (5.1)	2805 (3.4)	1173 (1.4)	465 (0.6)
2006/2007	2664 (3.4)	3049 (3.8)	815 (1.0)	334 (0.4)
2008/2009	1967 (2.6)	3176 (4.3)	623 (0.8)	284 (0.4)
2010/2011	1552 (2.3)	3113 (4.5)	538 (0.8)	238 (0.3)
2012/2013	1282 (2.1)	2956 (4.7)	421 (0.7)	193 (0.3)
2014/2015	954 (1.8)	2457 (4.6)	345 (0.7)	177 (0.3)

HT: hormone therapy

[a] other hormone therapy use includes injections, implants, and nasal administrations

Supplementary Table11. Hormone therapy in breast cancer patients stratified by administration route from 1996/1997 to 2014/2015

Years	Number of oral HT users (%)	Number of vaginal HT users (%)	Number of transdermal HT users (%)	Number of other[a] HT or mixed users (%)
1996/1997	778 (4.0)	556 (2.9)	195 (1.0)	104 (0.5)
1998/1999	970 (4.2)	671 (2.9)	233 (1.0)	125 (0.6)
2000/2001	1247 (4.7)	808 (3.0)	270 (1.0)	124 (0.5)
2002/2003	1408 (4.6)	940 (3.1)	294 (1.0)	138 (0.5)
2004/2005	957 (2.8)	1110 (3.2)	226 (0.7)	87 (0.3)
2006/2007	730 (1.9)	1284 (3.4)	193 (0.5)	82 (0.2)
2008/2009	594 (1.5)	1381 (3.4)	172 (0.4)	67 (0.2)
2010/2011	501 (1.2)	1404 (3.4)	138 (0.3)	59 (0.1)
2012/2013	466 (1.1)	1379 (3.3)	152 (0.4)	69 (0.2)
2014/2015	294 (0.8)	1175 (3.1)	135 (0.4)	47 (0.1)

HT: hormone therapy

[a] other hormone therapy use includes injections, implants, and nasal administrations

Supplementary File10. Numeric values corresponding to Figure4 of the main manuscript. Proportion of use of different hormone therapy doses over time in A) the cardiovascular disease and breast cancer sub-populations and B) the general UK female population

Supplementary Table12. Hormone therapy use in the general UK female population stratified by dose from 1996/1997 to 2014/2015

Years	Number of normal dose HT users (%)	Number of low dose HT users (%)	Number of mixed dose users (%)
1996/1997	149,909 (15.6)	11,786 (1.2)	18,339 (1.9)
1998/1999	165,331 (15.8)	16,368 (1.6)	21,760 (2.1)
2000/2001	176,053 (15.7)	22,729 (2.0)	27,394 (2.5)
2002/2003	162,046 (13.8)	26,674 (2.3)	30,162 (2.6)
2004/2005	104,445 (8.6)	27,655 (2.3)	24,213 (2.0)
2006/2007	79,159 (6.3)	30,294 (2.4)	23,171 (1.9)
2008/2009	69,728 (5.6)	32,455 (2.6)	18,551 (1.5)
2010/2011	59,273 (4.9)	35,740 (2.9)	17,623 (1.5)
2012/2013	51,602 (4.5)	35,795 (3.1)	15,424 (1.3)
2014/2015	41,403 (4.1)	32,622 (3.3)	13,388 (1.3)

HT: hormone therapy

Supplementary Table13. Hormone therapy in cardiovascular disease patients stratified by dose from 1996/1997 to 2014/2015

Years	Number of normal dose HT users (%)	Number of low dose HT users (%)	Number of mixed dose users (%)
1996/1997	7458 (10.8)	683 (1.0)	989 (1.4)
1998/1999	8724 (11.4)	928 (1.2)	1147 (1.5)
2000/2001	9777 (12.0)	1216 (1.5)	1456 (1.8)
2002/2003	9584 (11.5)	1479 (1.8)	1630 (2.0)
2004/2005	5938 (7.2)	1415 (1.7)	1238 (1.5)
2006/2007	4334 (5.5)	1516 (1.9)	1012 (1.3)
2008/2009	3702 (5.0)	1623 (2.2)	725 (1.0)
2010/2011	2937 (4.3)	1757 (2.5)	747 (1.1)
2012/2013	2465 (3.9)	1765 (2.8)	622 (1.0)
2014/2015	1891 (3.5)	1551 (2.9)	491 (0.9)

HT: hormone therapy

Supplementary Table14. Hormone therapy in breast cancer patients stratified by dose from 1996/1997 to 2014/2015

Years	Number of normal dose HT users (%)	Number of low dose HT users (%)	Number of mixed dose users (%)
1996/1997	1329 (6.9)	149 (0.8)	155 (0.8)
1998/1999	1617 (7.1)	209 (0.9)	173 (0.8)
2000/2001	1837 (6.9)	337 (1.3)	275 (1.0)
2002/2003	2002 (6.5)	436 (1.4)	342 (1.1)
2004/2005	1563 (4.5)	483 (1.4)	334 (1.0)
2006/2007	1383 (3.6)	593 (1.6)	313 (0.8)
2008/2009	1271 (3.2)	690 (1.7)	253 (0.6)
2010/2011	1079 (2.6)	783 (1.9)	240 (0.6)
2012/2013	1030 (2.5)	806 (2.0)	230 (0.6)
2014/2015	754 (2.0)	721 (1.9)	176 (0.5)

HT: hormone therapy

Supplementary File11. Proportion of hormone therapy use stratified by drug type, administration route and dose in the breast cancer sub-population

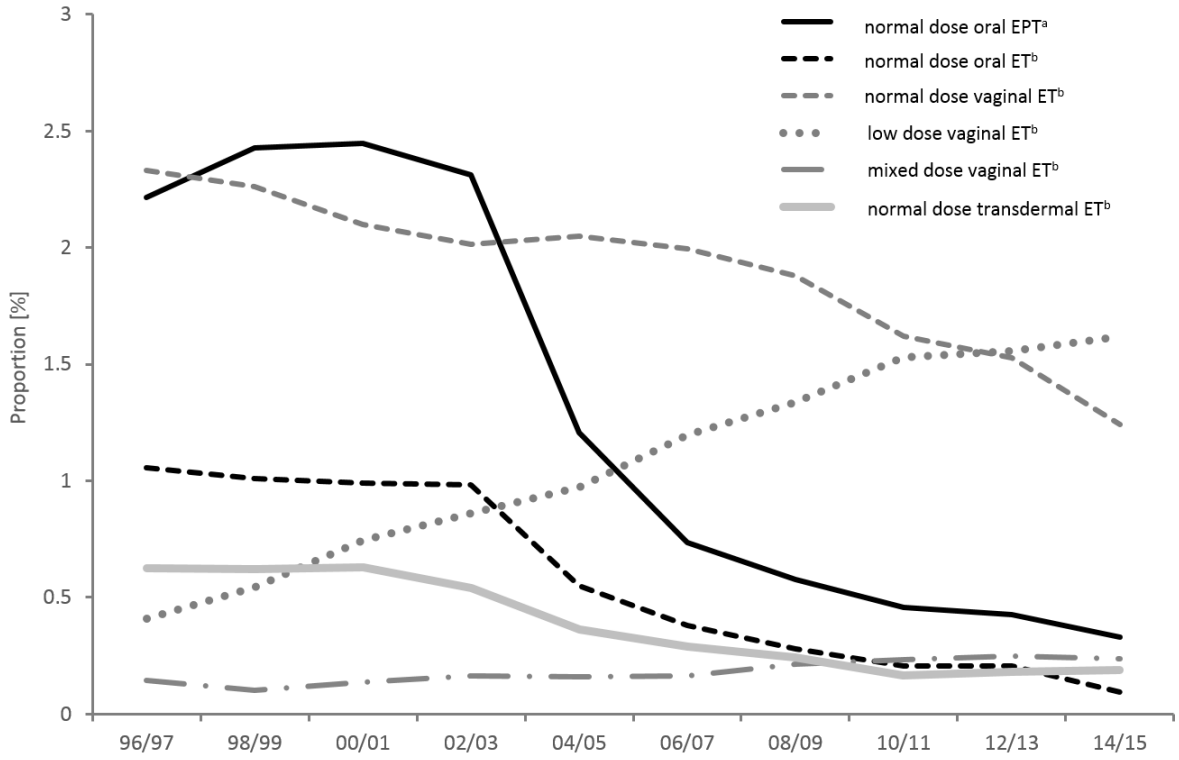
Supplementary Table15. Hormone therapy use stratified by drug type, administration route and dose in the breast cancer sub-population from 1996/1997 to 2014/2015

			Number of women (%)									
Drug type	Adm. route	Dose	96/97	98/99	00/01	02/03	04/05	06/07	08/09	10/11	12/13	14/15
EPT	Oral	Low	23 (0.12)	29 (0.13)	45 (0.17)	62 (0.20)	52 (0.15)	51 (0.13)	62 (0.15)	62 (0.15)	55 (0.13)	41 (0.11)
		Norm.	426 (2.21)	556 (2.43)	656 (2.45)	709 (2.31)	420 (1.21)	281 (0.74)	232 (0.58)	189 (0.46)	176 (0.43)	124 (0.33)
		Mixed	20 (0.10)	14 (0.06)	27 (0.10)	24 (0.08)	24 (0.07)	41 (0.11)	28 (0.07)	18 (0.04)	21 (0.05)	16 (0.04)
	Trans	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Norm.	43 (0.22)	59 (0.26)	61 (0.23)	81 (0.26)	54 (0.16)	38 (0.10)	36 (0.09)	38 (0.09)	36 (0.09)	32 (0.08)
		Mixed	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	5 (0.01)	N/A[b]	N/A[b]	N/A[b]	N/A[b]
	Vag.	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Norm.	N/A[b]	5 (0.02)	6 (0.02)	5 (0.02)	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Mixed	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
	Other [a]/ mixed use	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	5 (0.01)
		Norm.	36 (0.19)	47 (0.21)	45 (0.17)	45 (0.15)	18 (0.05)	18 (0.05)	13 (0.03)	11 (0.03)	13 (0.03)	9 (0.02)
		Mixed	17 (0.09)	12 (0.05)	14 (0.05)	16 (0.05)	9 (0.03)	21 (0.05)	14 (0.03)	16 (0.04)	18 (0.04)	9 (0.02)
ET	Oral	Low	25 (0.13)	30 (0.13)	58 (0.22)	64 (0.21)	58 (0.13)	49 (0.13)	49 (0.12)	56 (0.14)	62 (0.15)	33 (0.09)
		Norm.	203 (1.06)	231 (1.01)	265 (0.99)	301 (0.98)	191 (0.38)	145 (0.38)	113 (0.28)	86 (0.21)	86 (0.21)	36 (0.10)
		Mixed	6 (0.03)	6 (0.03)	6 (0.02)	9 (0.03)	14 (0.04)	17 (0.04)	8 (0.02)	6 (0.01)	8 (0.02)	11 (0.03)
	Trans	Low	21 (0.11)	20 (0.09)	24 (0.09)	33 (0.11)	25 (0.07)	30 (0.08)	28 (0.07)	26 (0.06)	31 (0.08)	22 (0.06)
		Norm.	120 (0.62)	142 (0.62)	169 (0.63)	166 (0.54)	126 (0.36)	111 (0.29)	98 (0.24)	68 (0.16)	75 (0.18)	72 (0.19)
		Mixed	10 (0.05)	10 (0.05)	13 (0.05)	12 (0.04)	19 (0.05)	9 (0.02)	7 (0.02)	6 (0.01)	10 (0.02)	6 (0.02)
	Vag.	Low	79 (0.41)	125 (0.55)	200 (0.75)	264 (0.86)	338 (0.97)	457 (1.20)	538 (1.34)	634 (1.53)	644 (1.56)	612 (1.62)
		Norm.	448 (2.33)	518 (2.26)	563 (2.10)	618 (2.01)	712 (2.05)	762 (1.99)	756 (1.88)	671 (1.62)	632 (1.53)	470 (1.24)
		Mixed	28 (0.15)	23 (2.26)	37 (0.14)	50 (0.16)	55 (0.16)	62 (0.16)	86 (0.21)	97 (0.23)	102 (0.25)	90 (0.24)
	Other [a]/ mixed use	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	5 (0.01)	N/A[b]	5 (0.01)	N/A[b]	N/A[b]	N/A[b]
		Norm.	32 (0.17)	31 (0.14)	29 (0.11)	31 (0.10)	20 (0.06)	14 (0.04)	13 (0.03)	8 (0.02)	9 (0.02)	7 (0.02)
		Mixed	12 (0.06)	14 (0.06)	13 (0.05)	21 (0.07)	20 (0.06)	20 (0.05)	12 (0.03)	13 (0.03)	14 (0.03)	8 (0.02)
Tib. and mixed use	Oral	Low	N/A[b]	N/A[b]	5 (0.02)	5 (0.02)	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Norm.	14 (0.07)	13 (0.06)	26 (0.10)	31 (0.10)	10 (0.03)	8 (0.02)	7 (0.02)	N/A[b]	N/A[b]	N/A[b]
		Mixed	61 (0.32)	90 (0.39)	159 (0.59)	203 (0.66)	187 (0.54)	136 (0.36)	94 (0.23)	81 (0.20)	56 (0.14)	31 (0.08)
	Trans	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Norm.	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Mixed	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
	Vag.	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Norm.	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Mixed	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
	Other [a]/ mixed use	Low	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	7 (0.02)	N/A[b]
		Norm.	6 (0.03)	15 (0.07)	17 (0.06)	15 (0.05)	9 (0.03)	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
		Mixed	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]

EPT: estrogen plus progestogen therapy, ET: estrogen therapy, Tib.: tibolone, Adm.: administration, Trans.: transdermal, Vag.: vaginal, Norm.: normal

[a] other HT: other hormone therapy use includes includes injections, implants, and nasal administrations

[b] N/A: not applicable as cell counts <5 are not reportable due to Medicines and Healthcare products Regulatory Agency (MHRA) regulations



Supplementary Figure17. Selected proportions of hormone therapy use stratified by drug type, administration route and dose in the breast cancer sub-population

[a]EPT: estrogen plus progestogen therapy

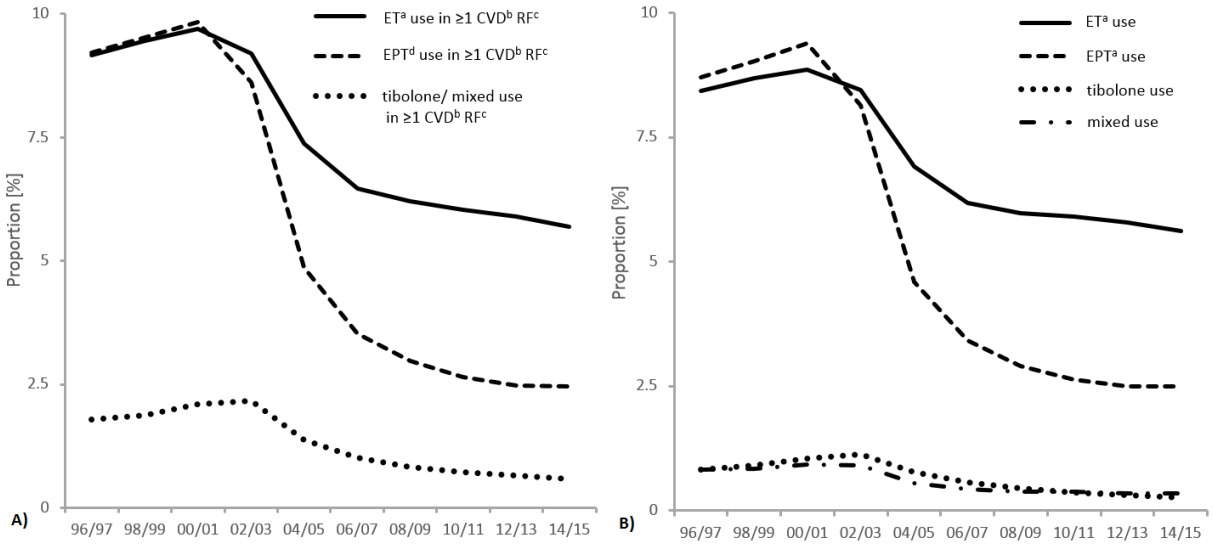
[b]ET: estrogen therapy

Supplementary File12. Hormone therapy use in the sub-population with ≥1 cardiovascular risk factor stratified by type, administration route and dose from 1996/1997 to 2014/2015

Supplementary Table16. Hormone therapy use in a population with ≥1 cardiovascular risk factors stratified by drug type from 1996/1997 to 2014/2015

Years	Number of ET users (%)	Number of EPT users (%)	Number of tibolone or mixed users (%)
1996/1997	44,184 (9.2)	44,417 (9.2)	8588 (1.8)
1998/1999	52,129 (9.5)	52,494 (9.5)	10,360 (1.9)
2000/2001	60,614 (9.7)	61,518 (9.8)	13,072 (2.1)
2002/2003	64,405 (9.2)	60,339 (8.6)	15,093 (2.2)
2004/2005	56,933 (7.4)	37,593 (4.9)	10,681 (1.4)
2006/2007	53,121 (6.5)	28,931 (3.5)	8346 (1.0)
2008/2009	51,489 (6.2)	24,684 (3.0)	6782 (0.8)
2010/2011	49,479 (6.0)	21,706 (2.7)	5921 (0.7)
2012/2013	46,350 (5.9)	19,452 (2.5)	5097 (0.7)
2014/2015	39,430 (5.7)	16,970 (2.5)	4087 (0.6)

ET: estrogen therapy, EPT: estrogen plus progestogen therapy



Supplementary Figure18. Proportion of use of different hormone therapy doses over time in A) a sub-population with ≥1 cardiovascular risk factor and B) the general UK female population

[a]ET: estrogen therapy

[b]CVD: cardiovascular disease

[c]RF: risk factor

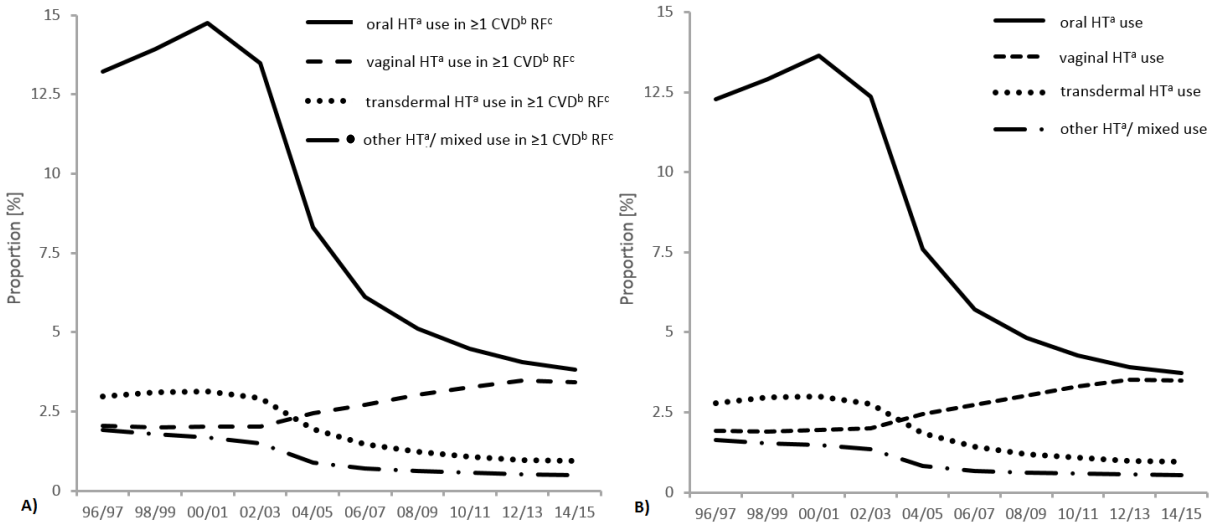
[d]EPT: estrogen plus progestogen therapy

Supplementary Table17. Hormone therapy use in a population with ≥1 cardiovascular risk factors stratified by administration route from 1996/1997 to 2014/2015

Years	Number of oral HT users (%)	Number of vaginal HT users (%)	Number of transdermal HT users (%)	Number of other[a] HT or mixed users (%)
1996/1997	63,733 (13.2)	9888 (2.1)	14,303 (3.0)	9265 (1.9)
1998/1999	76,912 (14.0)	11,015 (2.0)	17,166 (3.1)	9890 (1.8)
2000/2001	92,218 (14.8)	12,722 (2.0)	19,671 (3.2)	10,543 (1.7)
2002/2003	94,525 (13.5)	14,246 (2.0)	20,471 (2.9)	10,595 (1.5)
2004/2005	64,282 (8.3)	18,880 (2.4)	15,071 (2.0)	6974 (0.9)
2006/2007	50,119 (6.1)	22,332 (2.7)	12,044 (1.5)	5903 (0.7)
2008/2009	42,574 (5.1)	25,054 (3.0)	10,192 (1.2)	5135 (0.6)
2010/2011	36,707 (4.5)	26,708 (3.3)	8951 (1.1)	4740 (0.6)
2012/2013	31,894 (4.1)	27,220 (3.5)	7601 (1.0)	4184 (0.5)
2014/2015	26,528 (3.8)	23,818 (3.4)	6588 (1.0)	3553 (0.5)

HT: hormone therapy

[a] other hormone therapy use includes injections, implants, and nasal administrations



Supplementary Figure19. Proportion of use of different hormone therapy administration routes over time in A) a sub-population with ≥1 cardiovascular risk factor and B) the general UK female population

[a]HT: hormone therapy

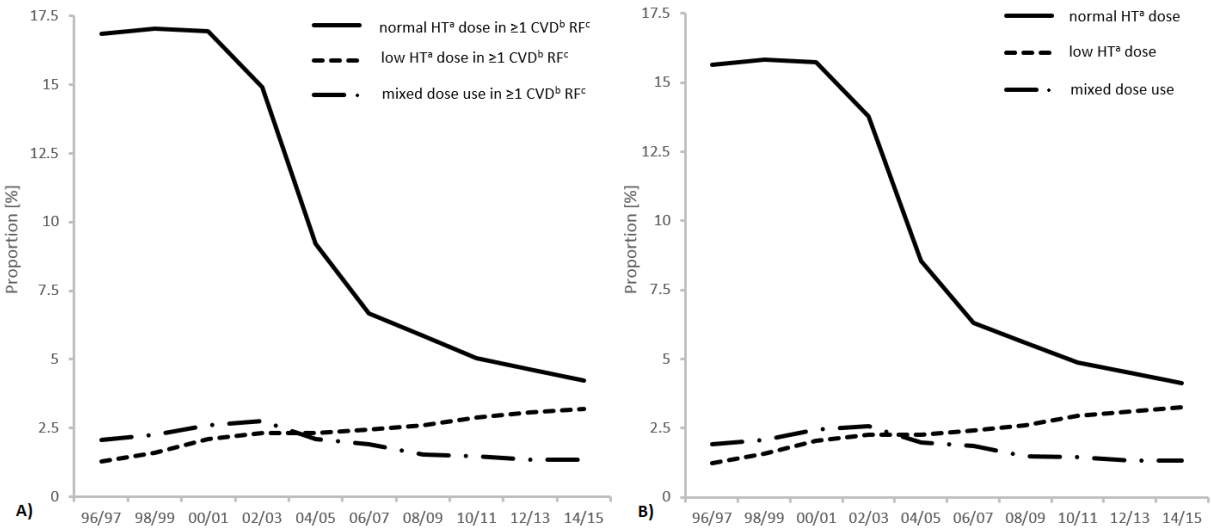
[b]CVD: cardiovascular disease

[c]RF: risk factor

Supplementary Table18. Hormone therapy use in a population with ≥1 cardiovascular risk factors stratified by dose from 1996/1997 to 2014/2015

Years	Normal HT dose use (%)	Low HT dose use (%)	Mixed dose use (%)
1996/1997	81,108 (16.8)	6139 (1.3)	9942 (2.1)
1998/1999	93,894 (17.0)	8739 (1.6)	12,350 (2.2)
2000/2001	105,926 (16.9)	13,003 (2.1)	16,275 (2.6)
2002/2003	104,328 (14.9)	16,326 (2.3)	19,183 (2.7)
2004/2005	71,201 (9.2)	17,816 (2.3)	16,190 (2.1)
2006/2007	54,756 (6.7)	19,928 (2.4)	15,714 (1.9)
2008/2009	48,720 (5.9)	21,643 (2.6)	12,592 (1.5)
2010/2011	41,425 (5.1)	23,692 (2.9)	11,989 (1.5)
2012/2013	36,233 (4.6)	24,080 (3.1)	10,586 (1.4)
2014/2015	29,186 (4.2)	22,093 (3.2)	9208 (1.3)

HT: hormone therapy



Supplementary Figure20. Proportion of use of different hormone therapy doses over time in A) a sub-population with ≥1 cardiovascular risk factors and B) the general UK female population
[a]HT: hormone therapy, [b]CVD: cardiovascular disease, [c]RF: risk factor

Supplementary File13. Numeric values corresponding to Figure5 of the main manuscript. Proportion of use of different hormone therapy administration routes in a sub-population with ≥1 cardiovascular risk factor stratified by number of risk factors

Supplementary Table19. Hormone therapy use in a population with ≥1 cardiovascular risk factors stratified by administration route and number of risk factors from 1996/1997 to 2014/2015

		Number of women (%)									
		96/97	98/99	00/01	02/03	04/05	06/07	08/09	10/11	12/13	14/15
Over.	0-1 RF	153,701 (18.8)	169,593 (19.5)	182,488 (20.2)	56,502 (18.5)	46,966 (12.8)	43,976 (10.7)	42,672 (9.8)	42,644 (9.5)	40,050 (9.2)	34,309 (9.0)
	2-3 RFs	25,527 (18.7)	32,595 (19.6)	41,603 (20.5)	47,078 (19.3)	37,565 (13.1)	33,229 (10.5)	31,557 (9.6)	29,829 (9.0)	28,077 (8.7)	24,314 (8.4)
	4-5 RFs	806 (16.5)	1271 (16.8)	2085 (17.1)	2854 (15.5)	2714 (10.2)	2684 (8.1)	2716 (7.4)	2672 (7.0)	2530 (6.6)	2283 (6.5)
Oral HT	0-1 RF	101,205 (12.4)	112,964 (13.0)	123,720 (13.7)	112,44 8 (12.3)	69,068 (7.6)	52,735 (5.8)	43,789 (5.0)	37,491 (4.4)	32,164 (4.1)	26,507 (3.9)
	2-3 RFs	16,056 (11.7)	21,148 (12.7)	27,777 (13.7)	31,251 (12.8)	22,305 (7.8)	17,487 (5.5)	15,183 (4.6)	13,353 (4.0)	11,845 (3.7)	9997 (3.5)
	4-5 RFs	437 (8.9)	778 (10.3)	1262 (10.3)	1768 (9.6)	1486 (5.6)	1301 (3.9)	1200 (3.3)	1050 (2.7)	871 (2.3)	738 (2.1)
Trans HT	0-1 RF	22,849 (2.8)	26,052 (3.0)	27,183 (3.0)	25,142 (2.8)	16,870 (1.9)	13,030 (1.4)	10,721 (1.2)	9405 (1.1)	7972 (1.0)	6898 (1.0)
	2-3 RFs	3772 (2.8)	4857 (2.9)	6026 (3.0)	7008 (2.9)	5388 (1.9)	4476 (1.4)	3913 (1.2)	3430 (1.0)	2986 (0.9)	2559 (0.9)
	4-5 RFs	158 (3.2)	213 (2.8)	348 (2.9)	470 (2.6)	417 (1.6)	334 (1.0)	294 (0.8)	278 (0.7)	251 (0.7)	223 (0.6)
Vag. HT	0-1 RF	15,151 (1.9)	15,762 (1.8)	16,676 (1.8)	17,556 (1.9)	21,678 (2.4)	24,047 (2.7)	25,967 (3.0)	27,717 (3.3)	27,249 (3.5)	23,322 (3.4)
	2-3 RFs	3247 (2.4)	3795 (2.3)	4703 (2.3)	5511 (2.3)	7566 (2.6)	9253 (2.9)	10,653 (3.2)	11,349 (3.4)	11,728 (3.6)	10,451 (3.6)
	4-5 RFs	138 (2.8)	178 (2.4)	314 (2.6)	418 (2.3)	661 (2.5)	927 (2.8)	1098 (3.0)	1230 (3.2)	1316 (3.4)	1225 (3.5)
Other[a]/ mixed use	0-1 RF	14,496 (1.8)	14,815 (1.7)	14,909 (1.7)	13,804 (1.5)	8418 (0.9)	6899 (0.8)	5984 (0.7)	5522 (0.7)	4829 (0.6)	4089 (0.6)
	2-3 RFs	2452 (1.8)	2795 (1.7)	3097 (1.5)	3308 (1.4)	2306 (0.8)	2013 (0.6)	1808 (0.6)	1697 (0.5)	1518 (0.5)	1307 (0.5)
	4-5 RFs	73 (1.5)	102 (1.4)	161 (1.3)	198 (1.1)	150 (0.6)	122 (0.4)	124 (0.3)	114 (0.3)	92 (0.2)	97 (0.3)

Over.: overall, Trans.: trandsdermal, Vag.: vaginal, RF: risk factor
[a] other: hormone therapy use includes injections, implants, and nasal administrations

8.2 Appendix 2

Risk of hand osteoarthritis in new users of hormone replacement therapy:

A nested case-control analysis

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Objective: To estimate the risk of hand osteoarthritis (HOA) associated with hormone replacement therapy (HRT).

Methods: We conducted a nested case-control study using data from the UK-based Clinical Practice Research Datalink (1998-2017). In women entering at age 45 (inception cohort), we matched women with incident HOA during follow-up (cases) 1:4 to osteoarthritis-free controls on age and calendar date (index date, ID). We applied conditional logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) of HOA associated with new HRT use compared to non-use overall and in women with recorded menopause, in whom, we calculated separate ORs subdivided by time between menopause and HRT initiation (current users), and by time between HRT cessation and the ID (past users), versus non-users.

Results: Among 3440 cases and 13,760 controls (mean age: 50.9±4.1 years), we observed an adjusted OR (aOR) of HOA of 1.32 (95% CI 1.17-1.48) in HRT users (versus non-users), which attenuated to 0.98 (95% CI 0.85-1.14) in women with recorded menopause. Current users (versus non-users), who initiated HRT within 3 months before/after menopause, had an aOR of 0.72 (95% CI 0.55-0.96), while aORs increased with later HRT initiation. Among past users (versus non-users), we observed an aOR of 1.25 (95% CI 0.86-1.81) when HRT use was stopped ≤18 months before the ID, approaching the null with increasing duration between HRT cessation and the ID.

Conclusion: Current HRT use was associated with a decreased risk of HOA if initiated around menopause, but the risk reduction disappeared after HRT cessation.

Keywords: hormone replacement therapy; hand osteoarthritis; menopause; epidemiology

INTRODUCTION

Hand osteoarthritis is a degenerative disease characterised by joint pain and bony enlargements/ swellings, occurring most frequently in postmenopausal women and the elderly.[1,2] To date, no disease-modifying treatment is available.[3] The exact etiology of osteoarthritis is unknown, but the increase in incidence of hand osteoarthritis in postmenopausal women and the presence of estrogen receptors in cartilage suggest that hormone replacement therapy (HRT) may help preventing the development of osteoarthritis.[4]

Preclinical studies mainly assessed the effect of HRT on knee osteoarthritis and yielded contradictory results.[5] Mechanical stress is a major risk factor for osteoarthritis of weight-bearing joints (i.e. knee, hip)[6], which is often not adequately controlled for. Hand osteoarthritis is minimally affected by mechanical factors and thus a more suitable outcome to assess the association between osteoarthritis and systemic exposures. However, small cross-sectional studies investigating the association between HRT and hand osteoarthritis or generalized osteoarthritis (≥3 joints affected, usually includes hand osteoarthritis) also yielded contradictory results.[7-11] A descriptive study reported that 55% of women who developed hand osteoarthritis after menopause developed it within 4 years after menopause.[12] Thus, timing of HRT use relative to menopause and/or hand osteoarthritis may play an important role in the association between HRT use and hand osteoarthritis, but has not been studied yet.

In this nested case-control analysis we investigated the association of new HRT use on the risk of incident hand osteoarthritis overall and stratified by timing of HRT use. Furthermore, we assessed the timing of HRT initiation and cessation relative to recorded menopause and diagnoses of hand osteoarthritis, respectively.

PATIENTS AND METHODS

Study design and Data source

We conducted a nested case-control study using data derived from Clinical Practice Research Datalink (CPRD) GOLD which comprises de-identified primary care data of more than 11.3 million patients.[13] General practitioners (GP) act as gatekeepers within the National Health Service (NHS) and electronically record information on diagnoses, prescriptions, medical symptoms, laboratory values, referrals to secondary care, demographics, and lifestyle factors (e.g. body mass index [BMI], smoking status).[14] Prescriptions are (nearly) completely recorded and diagnoses have been repeatedly shown to be of high validity.[15] We further used CPRD-linked patient level data on socio-economic status (index of multiple deprivation, IMD), which is available for patients living in England only.[16,17] The interpretation and conclusions contained in this study are those of the authors alone.

Study population

We included all women on July 1st (cohort entry) of the year in which they turned 45 years old (based on their year of birth) between January 1998 and December 2017 in an inception cohort. We excluded all women with ≤1 year of active history and/or <1 GP visit on the database prior to cohort entry. We further excluded women with a history of hand osteoarthritis and with diseases potentially linked to secondary osteoarthritis or differential diagnoses of hand osteoarthritis prior to cohort entry, namely hemarthrosis of the hand, malformation or misalignments of the fingers, hypermobility syndrome, hyperparathyroidism, acromegaly, previous finger injury (e.g. fracture, dislocation, tear of ligament), Stickler syndrome, Paget's disease, disorder of iron metabolism (hemochromatosis), inflammatory polyarthropathies, and Wilson disease.[18,19] Women were not eligible if they had a recorded

Read code[13] for any cancer (except non-melanoma skin cancer), alcoholism, alcohol/ other substance abuse, or HIV/ AIDS at any time prior to cohort entry. Furthermore, women were excluded if they used systemic HRT prior to cohort entry.

Follow-up and case definition/ validity

We followed all women from cohort entry until they developed incident symptomatic hand osteoarthritis (cases) defined as 1) a first-time Read code of hand osteoarthritis or 2) a Read code of hand pain if followed by an incident Read code of hand osteoarthritis, osteoarthritis, or generalized osteoarthritis (Read codes in Supplemental File 1) within 365 days thereafter. The case index date was defined as the first record of either first-time hand osteoarthritis or hand pain. Follow-up was censored at the first of the following: recorded exclusion criterion described above (except for first-time systemic HRT use), disenrollment from the CPRD, age 65, or the end of the study period (December 2017).

As hand osteoarthritis is a diagnosis mainly made in primary care, we could not validate diagnoses using secondary care data. Nonetheless, in a sensitivity analysis, we restricted cases to women with a diagnosis of incident hand osteoarthritis that was preceded or followed by a specialist referral/ discharge (rheumatologist/ orthopaedist/ radiologist), or diagnostic work up (MRI, X-ray, ultrasonography) within 90 days before or after the diagnosis (19.1% of cases). In a further sensitivity analysis, to account for the slowly developing character of hand osteoarthritis potentially leading to a delayed diagnosis, we reanalysed the data with the index date shifted to 180 days before the hand osteoarthritis diagnosis date or matched date in controls. Women with ≤180 days of follow-up were excluded from this analysis.

Definition of controls

Each hand osteoarthritis case was matched to four controls from the study population who did not have a record of hand osteoarthritis up to 180 days prior to the case index date (risk-set sampling with a lag period to account for gradual disease onset) on age, calendar date (case index date), GP practice, and years of history in the CPRD before the index date.

Exposure

We defined new HRT use as a first ever recorded prescription for any systemic opposed or unopposed HRT. We included systemic formulations (i.e. oral, transdermal, topical, nasally administered, implanted, or injected formulations), but not vaginal formulations due to their relatively low, variable systemic bioavailability.

A woman was considered exposed from the day after the first HRT prescription, and was considered "currently exposed" for as long as each prescription was followed by a subsequent prescription within a grace period of 180 days after the alleged end of supply (Figure 1). Supply length was determined based on the number of prescribed products and dose instructions. In case of missing or improbable information on supply length, we used previously assessed default values of product quantities and dosing (Supplemental File 2). A person was classified as having past exposure from day 181 after a current prescription supply ended (Figure 1). Past users were censored whenever a new systemic HRT prescription was recorded (i.e. past users could not become current users again).

Covariates

We captured the following potential confounders of the association between HRT initiation and hand osteoarthritis (selected *a priori* based on clinical knowledge) recorded at any time before the index date (if not specified otherwise): BMI ≥30 kg/m^2 (Read code or measure for

BMI),[7,8,10,20,21] current smoking,[8,10,11] heavy alcohol consumption >14 units/week,[10] osteoporosis (Read code or prescription for bone-modifying drug),[7,20] diabetes (Read code or antidiabetic drug), thiazide prescriptions,[8] dyslipidemia (Read code or laboratory value), a vaccination record (proxy for health care seeking behavior), and >5 GP contacts[21] within the year prior to cohort entry (proxy for health care seeking behavior; we assessed GP contacts prior to cohort entry because assessing GP contacts prior to the index date would lie on the causal pathway between HRT initiation and hand osteoarthritis). With dichotomization of lifestyle covariates, we assumed that women with a missing record of BMI (9.0%), smoking status (2.8%), or alcohol consumption (8.3%) were non-obese, non-smokers, or non-heavy drinkers.

Statistical analysis

We conducted multivariable conditional logistic regression analyses to estimate crude and adjusted odds ratios (OR, adjusted for all covariates listed under 2.6 Covariates) with 95% confidence intervals (CI) of the association between new HRT use compared to non-use and hand osteoarthritis overall, and stratified by timing of HRT use (currently exposed, past exposed). In additional analyses, we further adjusted for anytime vaginal HRT use (yes/no), and separately for socio-economic status in 60.2% of women with available information on IMD (in quintiles).

To assess confounding by whether or not a woman had menopause recorded in the database, we calculated crude and adjusted ORs of hand osteoarthritis in women with recorded menopause compared to women who had no menopause record (menopause records were assessed between cohort entry and the index date only, women with a menopause record before cohort entry were excluded). Because we observed an association between the

presence of recorded menopause and a diagnosis for hand osteoarthritis, we restricted the remainder of analyses to women with recorded menopause. In these women, we estimated ORs of the association between hand osteoarthritis and new HRT use, compared to non-use overall and stratified by timing of HRT use (currently exposed, past exposed). We further estimated ORs stratified by timing of HRT initiation relative to recorded menopause in current users compared to non-users (>3 months before menopause [range: 140-2811 days], ≤3 months before/after menopause, 3-36 months after menopause, and >36 months after menopause [range: 1126-4474 days]). Furthermore, we estimated ORs stratified by timing of HRT cessation before the index date among past users, compared to non-users (≤18 months before the index date, >18-54 months before the index date, and >54 months before the index date).

Moreover, to describe the temporal trend of hand osteoarthritis onset after menopause, we described the proportion of hand osteoarthritis cases in women with recorded menopause after cohort entry in 1-year intervals after recorded menopause. Proportions were estimated by dividing the number of hand osteoarthritis cases in each interval by the number of total hand osteoarthritis cases at any time between cohort entry and index date. We performed all analyses using SAS statistical software version 9.4 (NC, USA).

RESULTS

We identified 623,671 women who turned 45 years old during the study period. After application of exclusion criteria, we included 438,674 women in the inception cohort (Figure 2). Among this cohort, we identified 3440 hand osteoarthritis cases and 13,760 matched controls. Characteristics of cases and controls are displayed in Table 1. The mean age of cases and controls at the index date was 50.9 years (standard deviation: 4.1 years). Cases

had more recorded diagnoses of osteoporosis, diabetes, dyslipidemia, and obesity before the index date, and also saw their GP more often in the year prior to cohort entry, than controls.

The adjusted OR of hand osteoarthritis in HRT users compared to non-users was 1.32 (95% CI 1.17-1.48) [Table 2]. A record of menopause (irrespective of HRT use) was associated with an increased adjusted OR of hand osteoarthritis of 1.42 (95% CI 1.29-1.57) when compared to women without recorded menopause (Figure 3, crude ORs in Supplemental File 3). In women with recorded menopause, there was no association between HRT use and risk of hand osteoarthritis: adjusted OR 0.98 (95% CI 0.85-1.14) when compared to non-use (Figure 3, crude ORs in Supplemental File 3). Current HRT users, versus non-users, had a decreased adjusted OR of hand osteoarthritis of 0.72 (95% CI 0.55-0.96), when HRT was initiated within 3 months before/after menopause with ORs increasing with later HRT initiation. Of all current users 68% of women used oral EPT within 12 months prior to the index date. Women with past HRT use had a statistically non-significantly adjusted OR of hand osteoarthritis of 1.25 (95% CI 0.86-1.81) if HRT was stopped ≤18 months before the index date, which decreased towards the null with increasing duration between HRT cessation and the index date (Figure 3, crude ORs in Supplemental File 3).

The proportion of women with hand osteoarthritis diagnoses decreased with increasing number of 1-year intervals after recorded menopause. A maximum proportion of 18.4% of women had hand osteoarthritis recorded (158 of 860 cases) within 1 year after recorded menopause. Cumulatively, 54.9% and 79.9% of women had hand osteoarthritis recorded within 4 years and 7 years, respectively (Figure 4, Supplemental File 4).

In all analyses, adjusted ORs of hand osteoarthritis were lower in current and higher in past HRT users than when HRT was assessed overall (Table 2, Figure 3). When we further adjusted

the overall analysis for vaginal HRT use and socioeconomic status, results remained unchanged (Table 2). In sensitivity analyses related to outcome validity, results remained largely unchanged as well (Table 2).

DISCUSSION

In this nested case-control study embedded in an inception cohort of women aged 45 at entry, we assessed the risk of hand osteoarthritis in HRT users compared to non-users overall, stratified by timing of HRT, and in women with recorded menopause only. In women with recorded menopause only, we further investigated separate ORs subdivided by time between menopause and HRT initiation (current users), and by time between HRT cessation and the index date (past users), compared to non-users.

Previous small observational studies investigating the association between HRT and hand osteoarthritis, or generalized osteoarthritis, yielded contradictory results.[7-11] Though authors had access to hospital-based information on diagnosis, the cross-sectional study design prevented them from assessing temporality of HRT use in relation to hand osteoarthritis or menopausal status.[7-11] We observed a 32% increased risk of hand osteoarthritis in all HRT users when compared to non-users which attenuated to a null result after restriction to women with recorded menopause. We assumed that HRT use is a proxy for menopause onset in women without recoded menopause and therefore abstained from analyses in women without recorded menopause. Our results suggest that menopause is a risk factor for incident hand osteoarthritis (42% increased risk in our study). Other observational studies assessing the association between menopause with or without HRT use and hand osteoarthritis did not yield precise results mainly due to small sample sizes.[22] Watt et al. performed a small study (n=82) describing the association between menopause or HRT

cessation and onset of hand osteoarthritis symptoms in women in a UK secondary care clinic.[12] The authors reported a median duration between HRT cessation and onset of hand osteoarthritis of 6 months. We observed that, among women with recorded menopause who developed hand osteoarthritis, 55% of women did so within 4 years after menopause, the same proportion was reported by Watt et al..

Women who initiated HRT shortly before/after menopause were at a reduced risk of hand osteoarthritis (around 28% lower risk for women with current HRT use at the index date). We hypothesize that women who use systemic HRT to alleviate vasomotor symptoms may profit from a delayed onset or progression of hand osteoarthritis, when HRT is initiated around menopause and used continuously. Thus, our results support position statements of the North American Menopause Society[23] and International Menopause Society[24], which postulate a potential benefit of HRT on joint/ muscle pain and joint stiffness based on evidence from the well-known Women's Health Initiative reporting reduced arthroplasty and joint pain among unopposed oral HRT users[25,26], and reduced joint pain and stiffness among opposed oral HRT users[27], compared to non-users. To date, there is no information on the effect of progesterone alone or in conjunction with estrogen on articular cartilage. Our results also suggest that HRT cessation may slightly increase the risk of hand osteoarthritis (25% risk increase ≤18 months after cessation, based on small sample size), which may question the initial clinical benefit of HRT use. We hypothesize that hand osteoarthritis onset likely expressed by hand pain is similar to spontaneous exacerbation of vasomotor symptoms after HRT cessation.[23]

A strength of this study is its large population of more than 3'000 hand osteoarthritis cases among women observed longitudinally from age 45. Furthermore, we applied a new user design, allowing us to assess temporality of HRT use and hand osteoarthritis. Moreover, we

likely captured near complete HRT prescription information, as CPRD prescriptions are issued electronically by the GP. We do not know if women took all prescriptions. However, of women who had HRT prescribed during follow-up, 77.4% had >1 HRT prescription recorded, suggesting that most women filled their prescriptions repeatedly, and thus likely took the medication.

A major limitation of this study is the inconsistent recording of menopause in the CPRD. However, HRT use among women with recorded menopause in our study is consistent with numbers reported among the general UK female population (around 20-40% of women who have sought medical advice on menopause used HRT over time)[28,29]. Furthermore, as only around 30% of women with recorded menopause were prescribed HRT in our study, we hypothesize that women with a menopause record in the CPRD do not only represent women with severe postmenopausal symptoms but also women who had mild symptoms or whose menopause was recorded by chance. In our cohort, we suspect under recording of hand osteoarthritis (prevalence of 0.8%) because GPs may frequently lack to specify joint localization of osteoarthritis. However, by only including specific records of hand osteoarthritis we achieve a high specificity which is relevant for reliable risk estimation in comparative analyses. Yet, sample size of some strata in our study population was small and results have to be confirmed before drawing causal conclusions for clinical practice.

CONCLUSION

This nested case-control study yielded an increased risk of hand osteoarthritis in HRT users compared to non-users. This result was likely confounded by menopausal status, as the risk was attenuated after restriction to women with recorded menopause. Moreover, we observed a decreased risk of hand osteoarthritis in current HRT users who initiated HRT

around the time of the first menopause record. However, HRT cessation was temporarily associated with a slight risk increase of hand osteoarthritis.

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ETHICAL APPROVAL

This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The data is provided by patients and collected by the National Health Service as part of their care and support. The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (protocol 18_089R, made available to journal editors).

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SUPPLEMENTAL FILES

Supplemental File 1. Utilized Read codes for hand osteoarthritis diagnoses

Hand osteoarthritis diagnosis

N050100 Generalised osteoarthritis of the hand
N051400 Localised; primary osteoarthritis of the hand
N053400 Localised osteoarthritis; unspecified; of the hand
N054400 Oligoarticular osteoarthritis; unspecified; of hand
N05z400 Osteoarthritis NOS; of the hand
N05zF00 Osteoarthritis NOS; of MCP joint
N05zG00 Osteoarthritis NOS; of PIP joint of finger
N05zH00 Osteoarthritis NOS; of DIP joint of finger
N05z411 Finger osteoarthritis NOS
N052400 Localised; secondary osteoarthritis of the hand
2G26.00 O/E - hands - Heberden's nodes
N050111 Heberdens' nodes
N050700 Heberden's nodes with arthropathy
N050112 Bouchards' nodes
N050300 Bouchard's nodes with arthropathy
N05z412 Thumb osteoarthritis NOS
7K6ZG00 Injection of steroid into carpometacarpal joint of thumb
N051C00 Primary arthrosis of first carpometacarpal joints; bilateral
N052B00 Post-traumatic arthrosis of first carpometacarpal jt bilat
N053900 449 Arthrosis of first carpometacarpal joint; unspecified
Nyu2900 [X]Other primary arthrosis of first carpometacarpal joint
Nyu2A00 [X]Other post-traumatic arthrosis/1st carpometacarpal joint
Nyu2B00 [X]Other 2ndry arthrosis/1st carpometacarpal joints;bilaterl
Nyu2C00 [X]Other secondary arthrosis of first carpometacarpal joint
N03x600 Arthritis associated with other disease; MCP joint
N03x700 Arthritis associated with other disease; PIP joint of finger
N03x800 Arthritis associated with other disease; DIP joint of finger

N06z411 Hand arthritis NOS
N066400 Unspecified monoarthritis of the hand
N063400 Climacteric arthritis of the hand

Record of hand pain if followed by incident Read code of hand osteoarthritis (see above), osteoarthritis or generalized osteoarthritis (see below)

N245012 Finger pain
N245.14 Hand pain
N245000 Hand pain
N094400 Arthralgia of the hand
N094H00 Arthralgia of PIP joint of finger
N094J00 Arthralgia of DIP joint of finger
N245011 Thumb pain

(Generalized) Osteoarthritis diagnosis
N050400 Primary generalized osteoarthrosis
N050500 Secondary multiple arthrosis
N050600 Erosive osteoarthrosis
Nyu2000 [X]Other polyarthrosis
N050.00 Generalised osteoarthritis - OA
N050000 Generalised osteoarthritis of unspecified site
N050100 Generalised osteoarthritis of the hand
N050200 Generalised osteoarthritis of multiple sites
N050400 Primary generalized osteoarthrosis
N050z00 Generalised osteoarthritis NOS
N051.00 Localised; primary osteoarthritis
N051000 Localised; primary osteoarthritis of unspecified site
N051z00 Localised; primary osteoarthritis NOS
N052.00 Localised; secondary osteoarthritis
N052000 Localised; secondary osteoarthritis of unspecified site
N052z00 Localised; secondary osteoarthritis NOS
N053.00 Localised osteoarthritis; unspecified
N053000 Localised osteoarthritis; unspecified; of unspecified site
N053800 Localised osteoarthritis; unspecified; of other spec site
N053z00 Localised osteoarthritis; unspecified; NOS
N054.00 Oligoarticular osteoarthritis; unspecified
N054000 Oligoarticular osteoarthritis; unspec; of unspecified sites
N054400 Oligoarticular osteoarthritis; unspecified; of hand
N054800 Oligoarticular osteoarthritis; unspecified; other spec sites
N054900 Oligoarticular osteoarthritis; unspecified; multiple sites
N054z00 Osteoarthritis of more than one site; unspecified; NOS
N05z000 Osteoarthritis NOS; of unspecified site
N05z800 Osteoarthritis NOS; other specified site
N050500 Secondary multiple arthrosis
N050600 Erosive osteoarthrosis
Nyu2000 [X]Other polyarthrosis
N065A00 Generalised arthritis
Nyu2.00 [X]Arthrosis
Nyu2D00 [X]Other specified arthrosis
Nyu2F00 [X]Post-traumatic arthrosis of other joints

N05..00 Osteoarthritis and allied disorders
N05..11 Osteoarthritis
N050.00 Generalised osteoarthritis - OA
N05z.00 Osteoarthritis NOS
N05zz00 Osteoarthritis NOS
N06z.11 Arthritis
N063.00 Climacteric arthritis
N063.11 Menopausal arthritis
N094.00 Pain in joint - arthralgia
N094000 Arthralgia of unspecified site
N094800 Arthralgia of other specified site
N094900 Arthralgia of multiple joints
N094z00 Arthralgia NOS

Supplemental File 2. Exposure duration estimation and utilized (default) values in case of missing or improbable prescription quantities and/ or dosing instructions

In case of missing dosing instructions for hormone therapy (HT) products, we carried the last available value within the same patient of the same product code forward. If not available, we used the dosage of the last HT prescription within the patient if of the same administration type. If there was no previous information available, we used the following default values:

- Oral: 1 tablet per day
- Transdermal: 2 patches per week
- Topical gel in tube: 2 squirts of 1.25 grams of topical gel application per day
- Topical gel in sachets: 1 sachet of topical gel per day
- Nasal: 1 inhalation per nostril per day
- Injection: 1 injection per month
- Implant: An implant of 25 mg estrogen lasts 3 months, of 50 mg lasts 6 months, and of 100 mg lasts 10 months

Furthermore, we defined certain ranges and cut-offs of exposure lengths to correct potential typing/ spelling errors in the database.

Dose:

- Oral: if daily dose >6, we used the default value of 1 tablet per day
- Transdermal: if the daily dose was “biweekly” we used the default value of 2 patches per week (i.e. twice weekly)

In the CPRD, the variable of quantity (package size) is sometimes misused as number of packages. Therefore, we introduced ranges and cut-offs as follows:

- Oral: “1-3” = number of packages, “4-12” = number of 1-month packages (à 28 tablets), “13-364” = number of tablets, “>364”, we used the default value of 84 tablets per package
- Transdermal: “≤6” = number of 1-month packages (à 8 patches), “7-52” = number of patches, “>52”, we used the default value of 24 patches per package
- Topical gel in a tube: “≤8” = number of packages, “8-999” = weight in gram, “≥1000”, we divided the number by 100 and treated is as grams (these high numbers were likely due to a comma mistake)
- Topical gel in sachets: “≤3” = number of packages, “4-364” = number of sachets, “>364”, we used the default value of 28 sachets per package
- Nasal: “≤3” = number of packages, “4-7” = number of 1-month packages (à 60 nasal inhalations), “>7”, we used the default value of 180 nasal inhalations per package
- Injections: “≤1” = number of packages
- Implants: “≤1” = number of packages

If there were overlapping periods of HT prescriptions with the same product code the new current days were added at the end of the first period. If the overlapping periods were longer than 180 days the new period was added after this 180 days and everything that was left from the previous period was deleted. If there were overlapping periods with another product code, we followed them in parallel.

Supplemental File 3. Crude odds ratios corresponding to adjusted odds ratios of manuscript Figure 3

Supplementary Table1. Crude odds ratios of hand osteoarthritis in association with recorded menopause after cohort entry, and, in patients with recorded menopause after cohort entry, odds ratios of hand osteoarthritis in association with hormone therapy and stratified by timing of hormone therapy use (current/past use) and by timing of hormone therapy initiation relative to recorded menopause (in current users) and of hormone therapy cessation before the index date (in past users).

Patients with or without recorded menopause after cohort entry and before the index date	**Cases: 3085 (%)**	**Controls: 12,681 (%)**	**OR crude (95% CI)**	**OR adjusted* (95% CI)**
No recorded menopause	2225 (72.1)	10,071 (79.4)	1.00 ref	1.00 ref
Recorded menopause	860 (27.9)	2610 (20.6)	1.56 (1.42-1.72)	1.42 (1.29-1.57)
No HT use	604 (19.6)	1821 (14.4)	1.00 ref	1.00 ref
Overall HT use	256 (8.3)	789 (6.2)	0.97 (0.84-1.13)	0.98 (0.85-1.14)
Current HT use	106 (3.4)	378 (3.0)	0.88 (0.72-1.08)	0.85 (0.69-1.04)
… HT start >3 months before menopause	8 (0.3)	21 (0.2)	1.11 (0.55-2.23)	1.04 (0.52-2.09)
… HT start ≤3 months before/after menopause	55 (1.8)	238 (1.9)	0.75 (0.57-0.99)	0.72 (0.55-0.96)
… HT start 3-36 months after menopause	33 (1.1)	98 (0.8)	1.01 (0.71-1.44)	0.97 (0.68-1.37)

… HT start >36 months after menopause	10 (0.3)	21 (0.2)	1.30 (0.69-2.42)	1.30 (0.69-2.43)
Past HT use	150 (4.9)	411 (3.2)	1.07 (0.90-1.28)	1.10 (0.91-1.31)
… HT stop ≤18 months before the index date	29 (0.6)	64 (0.3)	1.25 (0.86-1.82)	1.25 (0.86-1.81)
… HT stop >18-54 months before the index date	65 (2.4)	170 (1.6)	1.11 (0.86-1.43)	1.11 (0.86-1.43)
… HT stop >54 months before the index date	56 (1.8)	177 (1.4)	0.97 (0.73-1.27)	1.01 (0.76-1.33)

OR: odds ratio, CI: confidence interval, HT: hormone therapy
*adjusted for osteoporosis, smoking, alcohol consumption, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use prior to index date and for number of GP contacts prior to cohort entry

Supplemental File 4. Numeric values corresponding to manuscript Figure 4

Supplementary Table2. Numeric values corresponding to manuscript Fig4. Proportion of hand osteoarthritis cases in 1-year intervals after recorded menopause

1-year intervals after recorded menopause	Number of hand osteoarthritis cases (total 860 cases)	Proportion of hand osteoarthritis cases in percentage terms (95% confidence interval)
1	158	18.4 (15.9-21.1)
2	114	13.3 (11.2-15.7)
3	101	11.7 (9.8-14.1)
4	99	11.5 (9.5-13.8)
5	86	10.0 (8.2-12.2)
6	77	9.0 (7.2-11.0)
7	52	6.1 (4.6-7.8)
8	51	5.9 (4.5-7.7)
9	32	3.7 (2.6-5.2)
10	30	3.5 (2.5-4.9)
11	17	2.0 (1.2-3.1)
12	15	1.7 (1.1-2.9)
13	12	1.4 (0.8-2.4)
14	11	1.3 (0.7-2.3)
15	2	0.2 (0.1-0.8)
16	2	0.2 (0.1-0.8)
17	0	0.0
18	1	0.1 (0.0-0.7)
19	0	0.0
20	0	0.0

8.3 Appendix 3

Appendix Table1. Numeric values corresponding to Fig3. Annual incidence rates of hormone replacement therapy use and hand osteoarthritis from 1996 to 2015

Year	No. of women with a first HRT prescr.	Obs. time in 100 py	Incidence rate of HRT use per 100 py (95% CI)	No. of women with a first hand OA diagnosis	Obs. time in 1'000 py	Incidence rate of hand OA per 1'000 py (95% CI)
1996	15910	3464.6	4.59 (4.52-4.66)	579	587.0	0.99 (0.91-1.07)
1997	14932	3688.6	4.05 (3.98-4.11)	664	629.9	1.05 (0.97-1.13)
1998	14443	3914.7	3.69 (3.63-3.75)	652	665.0	0.98 (0.91-1.06)
1999	15143	4139.5	3.66 (3.60-3.72)	663	695.5	0.95 (0.88-1.03)
2000	16442	4349.9	3.78 (3.72-3.84)	722	729.5	0.99 (0.92-1.06)
2001	16021	4495.9	3.56 (3.51-3.62)	945	757.0	1.25 (1.17-1.33)
2002	13753	4625.3	2.97 (2.92-3.02)	1044	784.3	1.33 (1.25-1.41)
2003	9790	4837.2	2.02 (1.98-2.06)	1286	807.0	1.59 (1.51-1.68)
2004	9625	5085.2	1.89 (1.85-1.93)	1466	830.7	1.76 (1.67-1.85)
2005	8476	5297.4	1.60 (1.57-1.63)	1531	848.5	1.80 (1.71-1.89)
2006	9047	5483.4	1.65 (1.62-1.68)	1520	859.7	1.77 (1.68-1.86)
2007	9346	5625.8	1.66 (1.63-1.69)	1569	867.6	1.81 (1.72-1.90)
2008	9630	5763.3	1.67 (1.64-1.70)	1706	872.7	1.95 (1.86-2.05)
2009	9735	5824.8	1.67 (1.64-1.70)	1728	866.1	2.00 (1.90-2.09)
2010	10133	5844.8	1.73 (1.70-1.77)	1692	850.1	1.99 (1.90-2.09)
2011	10176	5819.0	1.75 (1.71-1.78)	1611	830.6	1.94 (1.84-2.03)
2012	10095	5737.7	1.76 (1.73-1.79)	1585	814.0	1.95 (1.85-2.04)
2013	9610	5394.4	1.78 (1.75-1.82)	1490	766.8	1.94 (1.84-2.04)
2014	9117	4788.0	1.90 (1.87-1.94)	1280	681.9	1.88 (1.77-1.98)
2015	7680	3941.2	1.95 (1.91-1.99)	1049	567.5	1.85 (1.74-1.96)

No.: number, HRT: hormone replacement therapy, prescr.: prescription, Obs.: observation, py: person-years, CI: confidence interval, OA: osteoarthritis

8.4 Appendix 4

Appendix Table2. Numeric values corresponding to Fig4. Incidence rates of hormone replacement therapy use and of hand osteoarthritis stratified by age group

Age group [years]	No. of women with a first HRT prescr.	Obs. time in 100 py	Incidence rate of HRT use per 100 py (95% CI)	No. of women with a first hand OA diagnosis	Obs. time in 1'000 py	Incidence rate of hand OA per 1'000 py (95% CI)
40-44	25,871	25,711.1	1.01 (0.99-1.02)	1556	3098.4	0.50 (0.48-0.53)
45-49	64,286	22,413.7	2.87 (2.85-2.89)	2961	2956.7	1.00 (0.97-1.04)
50-54	73,067	16,475.1	4.43 (4.40-4.47)	4963	2762.6	1.80 (1.75-1.85)
55-59	33,421	11,983.8	2.79 (2.76-2.82)	5958	2457.3	2.42 (2.36-2.49)
60-64	18,792	10,609.5	1.77 (1.75-1.80)	5169	2163.3	2.39 (2.32-2.46)
65-69	13,667	10,927.2	1.25 (1.23-1.27)	4175	1872.7	2.23 (2.16-2.30)

No.: number, HRT: hormone replacement therapy, prescr.: prescription, Obs.: observation, py: person-years, CI: confidence interval, OA: osteoarthritis

8.5 Appendix 5

Appendix Table3. Numeric values corresponding to Fig5. Incidence rates of hormone replacement therapy use in women stratified by age group and study period

Study period	Age group [years]	No. of women with a first HRT prescription	Obs. time in 100 py	Incidence rate of HRT use per 100 py (95% CI)
1996-2002	40-44	13,177	7502.8	1.76 (1.73-1.78)
	45-49	31,883	5933.7	5.37 (5.31-5.43)
	50-54	32,795	4316.6	7.60 (7.51-7.68)
	55-59	13,523	3245.4	4.17 (4.10-4.24)
	60-64	8403	3489.1	2.41 (2.36-2.46)
	65-69	6863	4190.9	1.64 (1.60-1.68)
2003-2015	40-44	12,694	18,208.3	0.70 (0.69-0.71)
	45-49	32,403	16,471.0	1.97 (1.94-1.99)
	50-54	40,272	12,158.5	3.31 (3.28-3.34)
	55-59	19,898	8738.4	2.28 (2.25-2.31)
	60-64	10,389	7120.4	1.46 (1.43-1.49)
	65-69	6804	6736.3	1.01 (0.99-1.03)

No.: number, HRT: hormone replacement therapy, Obs.: observation, py: person-years,
CI: confidence interval, OA: osteoarthritis

8.6 Appendix 6

Appendix Table4. Numeric values corresponding to Fig6. Incidence rates of hand osteoarthritis in women stratified by age group and study period

Study period	Age group [years]	No. of women with a first hand OA diagnosis	Obs. time in 1'000 py	Incidence rate of hand OA per 1'000 py (95% CI)
1996-2002	40-44	377	983.5	0.38 (0.34-0.42)
	45-49	698	935.6	0.75 (0.69-0.80)
	50-54	1273	934.5	1.36 (1.29-1.44)
	55-59	1210	751.8	1.61 (1.52-1.70)
	60-64	927	643.7	1.44 (1.35-1.53)
	65-69	784	599.1	1.31 (1.22-1.44)
2003-2015	40-44	1179	2114.9	0.56 (0.53-0.59)
	45-49	2263	2021.2	1.12 (1.07-1.17)
	50-54	3690	1828.2	2.02 (1.95-2.08)
	55-59	4748	1705.5	2.78 (2.70-2.86)
	60-64	4242	1519.6	2.79 (2.71-2.88)
	65-69	3391	1273.7	2.66 (2.57-2.75)

No.: number, OA: osteoarthritis, Obs.: observation, py: person-years,
CI: confidence interval

8.7 Appendix 7

Appendix Table5. Array approach assessing residual confounding needed to increase the observed adjusted odds ratio (=relative risk) of 0.72 to 1.0 in hormone replacement initiators ≤3 months before/after recorded menopause who were still hormone replacement users at the index date

Observed adjusted RR*	Unmeasured confounder strength (RR)†	Unmeasured confounder prevalence in HRT users	Unmeasured confounder prevalence in non-users	RR additionally adjusted for unmeasured confounder	% Bias
0.72	1.0	0.00	0.15	**0.7**	0.00
0.72	1.5	0.00	0.15	**0.8**	-9.09
0.72	2.0	0.00	0.15	**0.9**	-16.67
0.72	2.5	0.00	0.15	**0.9**	-23.08
0.72	**3.0**	**0.00**	**0.15**	**1.0**	**-28.57**
0.72	3.5	0.00	0.15	**1.1**	-33.33
0.72	4.0	0.00	0.15	**1.2**	-37.50
0.72	4.5	0.00	0.15	**1.2**	-41.18
0.72	5.0	0.00	0.15	**1.3**	-44.44
0.72	5.5	0.00	0.15	**1.4**	-47.37
0.72	1.0	0.05	0.15	**0.7**	0.00
0.72	1.5	0.05	0.15	**0.8**	-6.82
0.72	2.0	0.05	0.15	**0.8**	-12.50
0.72	2.5	0.05	0.15	**0.9**	-17.31
0.72	3.0	0.05	0.15	**0.9**	-21.43
0.72	**3.5**	**0.05**	**0.15**	**1.0**	**-25.00**
0.72	4.0	0.05	0.15	**1.0**	-28.13
0.72	4.5	0.05	0.15	**1.0**	-30.88
0.72	5.0	0.05	0.15	**1.1**	-33.33
0.72	5.5	0.05	0.15	**1.1**	-35.53
0.72	1.0	0.10	0.15	**0.7**	0.00
0.72	1.5	0.10	0.15	**0.8**	-4.55
0.72	2.0	0.10	0.15	**0.8**	-8.33
0.72	2.5	0.10	0.15	**0.8**	-11.54
0.72	3.0	0.10	0.15	**0.8**	-14.29
0.72	3.5	0.10	0.15	**0.9**	-16.67
0.72	4.0	0.10	0.15	**0.9**	-18.75
0.72	4.5	0.10	0.15	**0.9**	-20.59
0.72	5.0	0.10	0.15	**0.9**	-22.22
0.72	5.5	0.10	0.15	**0.9**	-23.68

OR: odds ratio, RR: relative risk (or rate ratio), HRT: hormone replacement therapy

* relative risk of hand osteoarthritis of hormone replacement therapy initiators ≤3 months before/after recorded menopause who were still hormone replacement therapy users at the index date, compared to non-initiators, adjusted for osteoporosis, smoking, alcohol consumption, diabetes, thiazide prescriptions, dyslipidemia, obesity, vaccine use prior to index date and for number of GP contacts prior to cohort entry

† relative risk of hand osteoarthritis and unmeasured confounder compared to no unmeasured confounder

8.8 Appendix 8

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ORIGINAL ARTICLE

Risk of Incident Osteoarthritis of the Hand in Statin Initiators: A Sequential Cohort Study

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Objective. To investigate the association between statin therapy initiation and incident hand osteoarthritis (OA).
Methods. We performed a propensity score–matched cohort study using data from the UK-based Clinical Practice Research Datalink. Statin initiators had ≥1 statin prescription between 1996 and 2015 and were matched 1:1 on their propensity score to noninitiators within 10 sequential 2-year cohort entry blocks. After a 180-day run-in period, patients were followed in an as-treated approach until a recorded diagnosis of hand OA or until censoring (change in exposure status, development of an exclusion criterion, or maximum follow-up of 5.5 years). We applied Cox proportional hazard regression to calculate hazard ratios (HRs) with 95% confidence intervals (95% CIs) overall and in subgroups of sex, age, statin dose, statin agent, preexisting dyslipidemia, and treatment duration. To compare results, we ran all analyses with negative and positive control outcomes and assessed generalized OA as a secondary outcome. We further performed the overall analysis with an active comparator (topical glaucoma therapy initiators).
Results. Among 233,608 statin initiators and the same number of noninitiators, we observed an overall HR for hand OA of 0.98 (95% CI 0.88–1.09). The observed null result remained unchanged in all subgroups. Results were highly similar for generalized OA and negative control outcomes. In addition, the active comparator analysis showed a null result with an HR for hand OA of 0.85 (95% CI 0.56–1.29). Previously known associations with positive control outcomes were observed.
Conclusion. There was no association between statin initiation and incident hand OA in this study.

INTRODUCTION

Few effective treatments are currently available for hand osteoarthritis (OA), a painful and slowly developing chronic disease most frequently diagnosed in postmenopausal women and the elderly (1–4). Preclinical evidence suggests a protective effect of statins on osteoarthritic tissue, possibly mediated via pleiotropic antiinflammatory properties (5–8). However, observational studies are divided over whether this potential effect translates into clinical benefit (9–12). To date, studies have primarily assessed statin use and OA in any joint, not taking into account that systemic inflammation likely plays a stronger role in the pathomechanism of OA in non–weight-bearing joints (e.g., hand or fingers) compared to weight-bearing joints (e.g., knee or hip) (13). In addition, there is more potential for unmeasured confounding through mechanical factors when studying OA in weight-bearing compared with non–weight-bearing joints using electronic databases.

A previous case–control study conducted by Valdes et al (14) assessed the association of statin use and OA in non–weight-bearing joints. Their UK-based secondary care data included radiographic joint assessment, but statin use was captured as a crude dichotomous variable (current versus past use or never use) (14). The authors reported a decreased prevalence of generalized OA (systemic disease with ≥3 joints affected) but not of OA in single large joints or of nodal OA (a subtype of hand OA) in statin users compared to nonusers (14). We conducted a large observational cohort study to investigate the association between statin initiation and incident OA in non–weight-bearing joints

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Significance & Innovations

- Statin use was not associated with a reduced risk of hand osteoarthritis in this cohort study.
- Consistent results for several negative control outcomes corroborate this finding.
- Our results suggest that previous studies investigating the association of statin use and osteoarthritis of any joint might have been biased.

(primary outcome was hand OA; secondary outcome was generalized OA), using rigorous methodology to control for confounding.

PATIENTS AND METHODS

Study design and data source. We conducted a propensity score (PS)–matched sequential cohort study, using data from the UK-based Clinical Practice Research Datalink (CPRD). The CPRD comprises anonymized primary care data of 11.3 million patients, who are representative of the UK population with regard to age and sex (15). Information is entered into the database by general practitioners (GPs), who act as gatekeepers within the UK National Health System. The CPRD contains information on diagnoses, medical symptoms, laboratory values, referrals to secondary care, demographics, and to some extent lifestyle factors (e.g., body mass index, smoking status, alcohol consumption). Furthermore, a virtually complete primary care–based drug prescription history is available, since prescriptions are issued digitally via computer software (16). The high validity of the CPRD has been demonstrated repeatedly, especially with regard to chronic diseases (17). The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database Research (protocol 16_092R2).

Study population. We identified all patients ages 45–84 years at any time between January 1996 and December 2015 in the CPRD and extracted their statin initiation episodes (those patients with ≥1 new prescription for atorvastatin, fluvastatin, pravastatin, rosuvastatin, or simvastatin) after a statin-free period of ≥3 years (to prevent prevalent user bias). We categorized patients into 1 of 10 two-year entry blocks according to the date of the first prescription (referred to as cohort entry) (Figure 1A). Within each entry block, we identified all patients who had no statin prescriptions but had ≥3 years of recorded statin-free history and ≥1 recorded GP encounter during the respective entry block, to ensure database activity. These patients were assigned a random entry date within the respective entry block (cohort entry) (Figure 1B). Patients could only contribute 1 episode (statin initiation or noninitiation) per entry block, but they could contribute multiple episodes throughout the study period in different entry blocks if eligibility criteria were fulfilled (i.e., follow-up time was counted multiple times for some patients). We subsequently refer to patients as statin initiators or noninitiators. We excluded patients with a Read code (17) for prior atherothrombotic events in favor of homogeneity of the study population (i.e., to focus on statin use for primary

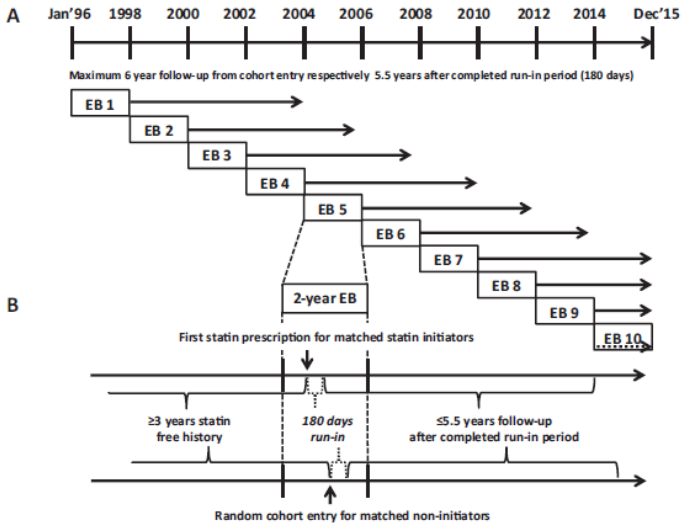

Figure 1. **A**, Study overview. Each entry block (EB) represented 1 cohort. The cohorts contained all eligible statin initiators and their 1:1 propensity score–matched noninitiators. We followed all statin initiators and noninitiators for a maximum of 6 years after their entry in an entry block, for 5.5 years after the completed run-in period, until they had a record of hand osteoarthritis (OA) or until they were censored. **B**, Entry block in detail. At least 3 years of statin-free history were required for both statin initiators and noninitiators to enter the cohort, and noninitiators additionally required ≥1 general practitioner encounter during the respective entry block. Matched statin initiators entered on the date of their first statin prescription; matched noninitiators entered on a random date. After a run-in period of 180 days, all statin initiators and noninitiators were followed up for a maximum of 5.5 years, until they had a record of hand OA, or they were censored.

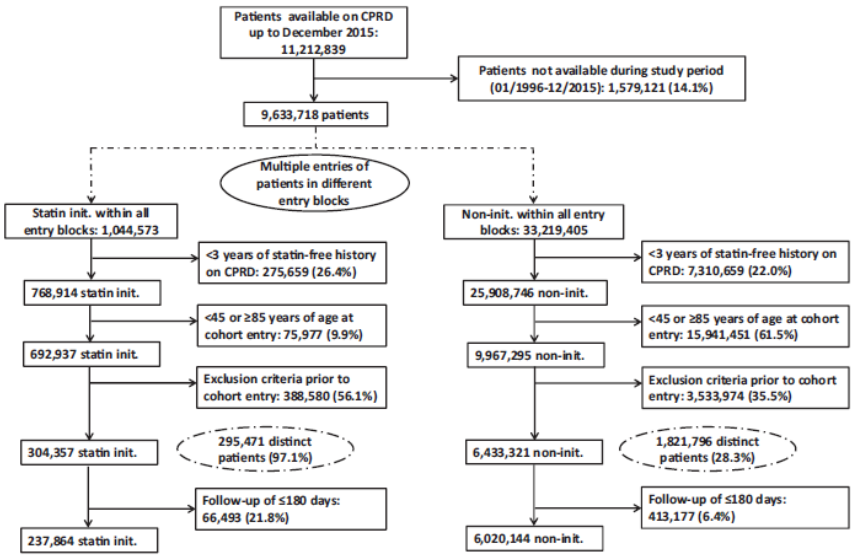

Figure 2. Flow chart of the study composition. CPRD = Clinical Practice Research Datalink; init. = initiators; non-init. = noninitiators.

prevention), but also because atherothrombotic events are a clear indication to initiate a statin, and patients who did not do so are likely to be a biased comparator group (18). Patients with strong risk factors for hand OA, such as preexisting OA of any joint, a disease associated with secondary OA, or a differential diagnosis of hand OA, were excluded, to minimize outcome misclassification (see Supplement 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract). We also excluded patients with alcoholism/substance abuse, HIV/AIDS, or a malignant cancer, because these patients are generally associated with a higher risk of bias and confounding in database studies. Patients with a previous prescription for cerivastatin (withdrawn from the market in 2001) were also excluded (a flow chart of the study population is shown in Figure 2) (19).

PS matching. We estimated a PS (probability of statin initiation) for each statin initiator and noninitiator, using multivariable logistic regression. We included characteristics recorded at any time before cohort entry, either those associated with the risk of developing hand OA only, or potential confounders of the association between statin initiation and hand OA (selected a priori based on clinical knowledge [20]) (Table 1). Prematching enrollment duration in the CPRD prior to the index date was comparable for statin initiators and noninitiators, with a mean ± SD duration of 11.9 ± 5.1 years for initiators and of 11.1 ± 5.3 years for noninitiators. Covariates included proxies for patient frailty (e.g., dysphagia, chronic diseases) (21) and health care–seeking behavior (e.g., the number of GP encounters ≤1 year prior to cohort entry) (22). To maximize comparability between matched pairs, we matched noninitiators to statin initiators within each of the 10 entry blocks separately (accounting for time-related bias due to changing statin prescribing patterns) (23). A generous 5-1 digit matching algorithm without replacement was applied, excluding those who could not be matched (24). In a sensitivity analysis, we trimmed our study population asymmetrically at the extreme ends of the PS tail (statin initiators below the 5th and noninitiators above the 95th percentile before matching) to exclude statin initiators and noninitiators treated contrary to prediction (25,26).

Follow-up. Follow-up started on day 181 after cohort entry (Figure 1B) to allow statin initiators to reach the maintenance dose and to account for the delay in diagnosis due to slow disease progression of hand OA (i.e., to reduce the probability of detecting prevalent hand OA cases during early follow-up). Exclusion of episodes of ≤180 days of follow-up also rule out inclusion of patients with poor statin adherence; studies have previously shown that a large proportion of patients discontinue statin treatment shortly after the first prescription (26,27). These early discontinuers might exhibit a higher risk of surveillance bias. We followed statin initiators and noninitiators in an as-treated approach until the first occurrence of a diagnosis of hand OA or censoring due to onset of an exclusion criterion described above, change of exposure status, disenrollment from the CPRD, December 2015, or maximum follow-up of 5.5 years after a completed run-in period. In a sensitivity analysis, we started follow-up on day 1 after cohort entry.

Exposure ascertainment. We defined continuous statin exposure during follow-up based on the estimated duration of supply of each recorded statin prescription, accounting for the number of tablets and dose instructions. A statin initiator was considered continuously exposed if a subsequent prescription was recorded ≤180 days after the alleged end of supply; if not, censoring occurred on the last day of supply of the last prescription. When prescription duration and/or dosage instructions were not recorded, we assumed

Table 1. Baseline characteristics of statin initiators and noninitiators (follow-up >180 days) before and after propensity score matching*

Characteristic	Before propensity score matching		Propensity score matched	
	Statin initiators (n = 237,864)	Noninitiators (n = 6,020,144)	Statin initiators (n = 233,608)	Noninitiators (n = 233,608)
Age, mean ± SD years	62.7 ± 9.4	58.0 ± 10.1	62.6 ± 9.4	63.2 ± 9.5
Follow-up, mean ± SD years	3.2 ± 2.0	3.7 ± 1.9	3.2 ± 2.0	3.1 ± 1.9
GP contacts ≤1 year before cohort entry, mean ± SD†	18.6 ± 11.9	9.9 ± 10.2	18.4 ± 11.8	19.5 ± 14.1
Women	116,938 (49.2)	3,483,217 (57.9)	115,046 (49.3)	117,550 (50.3)
Current smoker	47,940 (20.2)	1,196,042 (19.9)	47,132 (20.2)	47,081 (20.2)
Average alcohol intake >14 units/week	24,347 (10.2)	477,458 (7.9)	23,961 (10.3)	24,897 (10.7)
Comorbidities before cohort entry				
Obesity (BMI >30 kg/m^2)	69,683 (29.3)	1,037,949 (17.2)	67,833 (29.0)	68,867 (29.5)
Osteoporosis‡	7,567 (3.2)	134,992 (2.2)	7,465 (3.2)	8,696 (3.7)
Dyslipidemia§	173,648 (73.0)	1,215,270 (20)	169,524 (72.6)	173,951 (74.5)
Angina pectoris	20,416 (8.6)	91,707 (1.5)	19,362 (8.3)	17,358 (7.4)
Type 2 diabetes mellitus	42,980 (18.1)	112,698 (1.9)	39,879 (17.1)	35,069 (15.0)
Hypertension	119,142 (50.1)	1,087,893 (18.1)	116,315 (49.8)	123,385 (52.8)
Chronic ischemic heart disease	17,219 (7.2)	62,082 (1.0)	16,259 (7.0)	13,784 (5.9)
Congestive heart failure	3,981 (1.7)	33,509 (0.6)	3,818 (1.6)	3,930 (1.7)
Hypothyroidism	16,480 (6.9)	261,206 (4.3)	16,153 (6.9)	18,036 (7.7)
Vascular disease	9,139 (3.8)	84,084 (1.4)	8,784 (3.8)	8,890 (3.8)
Chronic kidney disease stage ≥3	11,696 (4.9)	82,649 (1.4)	11,484 (4.9)	12,168 (5.2)
Hip fracture	1,629 (0.7)	38,681 (0.6)	1,606 (0.7)	1,861 (0.8)
Liver disease	1,218 (0.5)	15,956 (0.3)	1,198 (0.5)	1,312 (0.6)
Macular degeneration	1,870 (0.8)	27,962 (0.5)	1,824 (0.8)	1,958 (0.8)
COPD	7,900 (3.3)	117,662 (2.0)	7,731 (3.3)	8,610 (3.7)
Anemia	12,614 (5.3)	347,545 (5.8)	12,399 (5.3)	14,232 (6.1)
Pressure ulcer/decubitus	1,902 (0.8)	31,160 (0.5)	1,847 (0.8)	2,019 (0.9)
Deep vein thrombosis	3,680 (1.6)	61,391 (1.0)	3,588 (1.5)	4,063 (1.7)
Dysphagia	3,607 (1.5)	66,164 (1.1)	3,553 (1.5)	3,997 (1.7)
≥1 hospitalization ≤1 year before cohort entry	37,127 (15.6)	532,036 (8.8)	36,342 (15.6)	38,447 (16.5)
Incontinence	4,934 (2.1)	94,007 (1.6)	4,846 (2.1)	5,549 (2.4)
Pneumonia	5,930 (2.5)	131,711 (2.2)	5,791 (2.5)	6,467 (2.8)
Psychotherapy¶	10,288 (4.3)	225,723 (3.8)	10,118 (4.3)	11,500 (4.9)
Delusional disorders	2,069 (0.9)	44,309 (0.7)	2,026 (0.9)	2,250 (1.0)
Comedication ≤180 days before cohort entry				
Hormone replacement therapy	14,660 (6.2)	503,190 (8.4)	14,483 (6.2)	16,007 (6.9)
Oral corticosteroids	8,695 (3.7)	156,474 (2.6)	8,498 (3.6)	9,626 (4.1)
Opioids	12,756 (5.4)	192,941 (3.2)	12,439 (5.3)	13,800 (5.9)
Fluoroquinolone antibiotics	2,648 (1.1)	49,183 (0.8)	2,595 (1.1)	2,957 (1.3)
Benzodiazepines	13,676 (5.8)	262,661 (4.4)	13,361 (5.7)	15,202 (6.5)
COPD drugs#	3,156 (1.3)	46,143 (0.8)	3,101 (1.3)	3,496 (1.5)
Coronary vasodilators	17,928 (7.5)	48,841 (0.8)	16,812 (7.2)	13,101 (5.6)
H_2 histamine antagonists	6,527 (2.7)	114,385 (1.9)	6,368 (2.7)	6,948 (3.0)
SSRIs	13,751 (5.8)	269,843 (4.5)	13,499 (5.8)	15,153 (6.5)
Other lipid-lowering agents	4,408 (1.9)	18,525 (0.3)	4,298 (1.8)	4,302 (1.8)
Cardiovascular drugs, no.**				
0	76,455 (32.1)	4,756,790 (79.0)	76,440 (32.7)	78,158 (33.5)
1–3	127,690 (53.7)	1,131,136 (18.8)	125,688 (53.8)	118,540 (50.7)
4–12	33,719 (14.2)	132,218 (2.2)	31,480 (13.5)	36,910 (15.8)

* Values are the number (%) unless indicated otherwise. GP = general practitioner; BMI = body mas index; COPD = chronic obstructive pulmonary disease; SSRIs = selective serotonin reuptake inhibitors.
† Only records on separate days.
‡ Defined as an osteoporosis diagnosis or intake of drugs affecting bone metabolism.
§ Defined as either a hyperlipidemia Read code or a laboratory value of low-density lipoprotein >3 mmoles/liter, of high-density lipoprotein <1 mmoles/liter, or of triglycerides >1.7 mmoles/liter.
¶ As a proxy for psychiatric disease.
# Defined as xanthines, long-acting inhaled anticholinergics including combinations, indacaterol, or aclidinium including combinations.
** Defined as angiotensin-converting enzyme inhibitor, angiotensin II receptor inhibitors, beta blockers, calcium channel blockers, diuretics, thrombocyte aggregation inhibitors, vitamin K antagonists, acetylsalicylic acid, other lipid-lowering agents, insulin, oral antidiabetic agents, or antiarrhythmic agents.

a 28-day supply (mode for statin prescriptions) and a regimen of 1 tablet/day, respectively.

Study designs using nonuser comparators may lead to surveillance bias as well as to differential follow-up and prognostic censoring, because nonadherence is only possible in the exposed population. Therefore, we further validated our results in 2 separate analyses, comparing statin initiators to active comparator groups of topical glaucoma therapy initiators (see the definition in Supplement 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract), and comparing initiators of ≥20 mg of simvastatin equivalents/day to initiators of <20 mg of simvastatin equivalents/day. Assuming similar health care–seeking behavior and a similar risk of nonadherence, these analyses accounted for such bias (26,28). For the glaucoma therapy versus statin analysis, patients were required to have been free of statin and glaucoma therapy for ≥3 years before cohort entry. In addition to previous censoring criteria, statin initiators were censored for starting glaucoma therapy and vice versa. We conservatively assumed that 1 prescription for glaucoma therapy lasted for 28 days. All other methods remained the same as in the main analysis.

Outcome. We defined hand OA as the first recorded Read code of primary or secondary OA of the fingers or hand (see Supplement 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract). We performed a sensitivity analysis restricted to hand OA diagnoses that were preceded by a diagnostic evaluation or specialist referral ≤180 days before the first diagnosis. Other hand OA Read codes led to censoring on the date of the hand OA diagnosis. To account for heterogeneity by delayed hand OA diagnoses, we shifted the first hand OA diagnosis to 180 days prior to the first recorded diagnosis. Cases with <360 days of initial follow-up were disregarded.

To further assess the validity of our findings with respect to surveillance bias (differential health care–seeking behavior), we defined a number of negative control outcomes (29) (cataract, peptic ulcer, psoriasis, tinnitus) (30–32). To validate our study population, we assessed 2 positive control outcomes (29) (myopathy [no run-in period applied] and a composite cardiovascular outcome, including death), which are well known to be associated with statin use (33,34). In a secondary analysis, we assessed generalized OA as the study outcome (see Supplement 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract). We did not assess generalized OA as a primary outcome due to limited capability to define generalized OA in CPRD data (35).

Statistical analysis. After combining all sequential cohorts into 1, we compared covariate distribution between treatment groups before and after PS matching. We performed Cox proportional hazards analyses, estimating hazard ratios (HRs) with 95% confidence intervals (95% CIs) for the association of hand OA and generalized OA separately, with statin initiation compared to noninitiation. The proportional hazard assumption was tested using the martingale residual method (held true overall and in subgroups of sex). We calculated crude HRs in PS deciles to assess heterogeneity of treatment effect across the PS distribution. For comparative reasons, we also ran all analyses using multivariable Cox regression in the unmatched cohort, adjusting for all covariates included in the PS. We performed subgroup analyses according to sex and age (45–64 and 65–84 years), daily statin dose (≤20 mg and >20 mg simvastatin equivalent versus noninitiators), individual statin (atorvastatin, simvastatin, other statins), and diagnosed preexisting dyslipidemia (i.e., a Read code of dyslipidemia or corresponding laboratory values), for which we rematched within subgroups. We further conducted subgroup analyses according to duration of follow-up (0–1, 2–3, 4–5.5 years) as a proxy for the cumulative statin dose, excluding those whose follow-up ended before the period of interest. The association between statin initiation and negative control outcomes was assessed identically, and the positive control outcomes were analyzed overall and in subgroups of duration of follow-up. We further estimated prematched and postmatching C statistics using a logistic regression model with all covariates that were included in the PS. This C statistic indicates the level of covariate balance between study groups, where 0.5 indicates perfect balance and 1.0 indicates maximal imbalance (36). All analyses were performed using SAS statistical software, version 9.4.

RESULTS

We identified 1,044,573 statin initiators and 33,219,405 noninitiators (potentially including multiple treatment episodes per patient) in the database during the study period. Characteristics of these patients are shown in Supplement 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract. After application of exclusion criteria, we identified 304,357 eligible statin initiators (295,471 individual patients [97.1%]) and 6,433,321 eligible noninitiators (1,821,796 individual patients [28.3%]). A total of 66,493 statin initiators (21.8%) and 413,177 noninitiators (6.4%) were further excluded due to ≤180 days of follow-up, resulting in 237,864 statin initiators and 6,020,144 noninitiators (PS distribution before PS matching [see Supplement 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract] and the flow chart of the study population [Figure 2]). Characteristics of statin initiators before and after applying exclusion criteria (see Supplement 7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract) were highly similar, with the prematching C statistic of C = 0.92 in the study population before applying exclusion criteria and C = 0.89 after applying exclusion criteria but before PS matching (Figure 2).

Of the 237,864 statin initiators, 98.2% were matched to noninitiators, resulting in 233,608 PS-matched pairs (231,092 individual patients among statin initiators [98.9%] and 183,644 individual patients among noninitiators [78.6%]). Before PS matching, the average age of statin initiators was older, and statin initiators had on average shorter follow-up (mainly due to differential censoring for change in exposure status) and were more likely to be men, more frequently hospitalized, and more frequently diagnosed with hypertension, type 2 diabetes mellitus (DM), or heart

Table 2. Association of statin initiation and incident hand osteoarthritis (OA) overall and in subgroups*

	Before propensity score matching				Propensity score matched		
	Time, statin initiators + noninitiators†	Hand OA events	Crude HR (95% CI)	Adjusted HR (95% CI)‡	Time, statin initiators + noninitiators†	Hand OA events	Matched HR (95% CI)‡
Overall	768.5 + 22,046.8	18,962	1.16 (1.08–1.25)	1.09 (1.01–1.18)	752.9 + 730.7	1,436	0.98 (0.88–1.09)
Sex							
Men	392.0 + 9,087.3	4,082	1.36 (1.19–1.55)	1.03 (0.89–1.19)	385.0 + 364.2	436	0.96 (0.79–1.15)
Women	376.5 + 12,959.5	14,880	1.22 (1.12–1.34)	1.10 (1.00–1.21)	365.4 + 365.8	977	1.03 (0.91–1.17)
Age, years							
45–64	446.8 + 16,836.3	14,822	1.19 (1.09–1.31)	1.10 (0.99–1.22)	433.6 + 431.4	876	1.02 (0.89–1.16)
65–84	321.7 + 5,210.6	4,140	1.18 (1.05–1.34)	1.12 (0.99–1.28)	314.6 + 297.7	549	0.95 (0.80–1.12)
Simvastatin equivalents, daily dose							
≤20 mg	467.1 + 22,046.8	18,648	1.09 (0.99–1.20)	1.03 (0.93–1.14)	465.2 + 441.8	837	0.95 (0.83–1.09)
>20 mg	301.3 + 22,046.8	18,542	1.27 (1.14–1.42)	1.19 (1.06–1.34)	301.2 + 299.0	619	1.02 (0.87–1.20)
Agent							
Atorvastatin	176.3 + 22,046.8	18,378	1.03 (0.88–1.21)	0.98 (0.83–1.15)	176.2 + 163.1	278	1.07 (0.85–1.36)
Simvastatin	531.3 + 22,046.8	18,761	1.22 (1.12–1.33)	1.15 (1.05–1.26)	529.8 + 517.5	1,059	0.99 (0.88–1.11)
Other statins	60.9 + 22,046.8	18,279	1.01 (0.77–1.33)	0.96 (0.73–1.27)	60.9 + 58.6	117	0.74 (0.52–1.07)
Indication for statin initiation							
Present dyslipidemia	555.5 + 3,638.3	4,328	1.02 (0.93–1.11)	1.10 (1.00–1.20)	536.9 + 513.5	1,106	1.01 (0.89–1.13)
Absent dyslipidemia	213.0 + 18,408.5	14,634	0.90 (0.77–1.06)	0.97 (0.82–1.14)	213.1 + 212.7	321	0.88 (0.70–1.09)
Duration of follow-up, years							
0–1	209.4 + 5,611.2	4,358	1.14 (0.98–1.33)	1.00 (0.86–1.18)	205.5 + 212.9	366	0.96 (0.78–1.18)
2–3	307.7 + 8,895.4	7,402	1.17 (1.04–1.32)	1.08 (0.96–1.23)	301.6 + 303.3	585	0.95 (0.81–1.12)
4–5.5	251.3 + 7,540.2	7,202	1.16 (1.03–1.31)	1.17 (1.02–1.34)	245.7 + 214.5	485	1.03 (0.87–1.24)
Active comparator analyses							
Glaucoma therapy (ref.)§	741.8 + 68.1	762	1.22 (0.93–1.62)	1.07 (0.79–1.45)	56.4 + 56.1	87	0.85 (0.56–1.29)
High-dose vs. low-dose statin initiators (ref.)¶	301.3 + 467.1	734	1.17 (1.01–1.35)	1.16 (1.00–1.35)	240.1 + 236.9	498	1.02 (0.85–1.21)
Sensitivity analyses							
Outcome validity#	768.5 + 22,046.8	2,206	1.37 (1.12–1.68)	1.15 (0.93–1.43)	752.9 + 730.7	204	0.93 (0.70–1.22)
Trimmed population**	732.0 + 21,117.6	18,011	1.18 (1.10–1.28)	1.12 (1.03–1.22)	347.9 + 367.4	722	0.95 (0.83–1.10)
Outcome shift††	768.5 + 22,046.3	16,743	1.17 (1.08–1.27)	1.13 (1.03–1.23)	752.6 + 731.3	1,215	1.08 (0.96–1.21)
Not adjusting for other lipid-lowering agents	768.5 + 22,046.8	18,962	1.16 (1.08–1.25)	1.09 (1.01–1.18)	753.5 + 731.1	1,454	0.95 (0.86–1.05)

* HR = hazard ratio; 95% CI = 95% confidence interval; ref. = reference.
† Observation time in 1,000 person-years.
‡ Adjusted for, and propensity score estimation with, all covariates (Table 1).
§ Topical glaucoma therapy initiators as active comparators to statin initiators.
¶ >20 mg simvastatin equivalent initiation (medium or high dose) versus ≤20 mg simvastatin equivalent initiation (low dose).
# Only including hand OA diagnoses that were preceded by a diagnostic evaluation (magnetic resonance imaging, radiograph, or ultrasonography) or a referral/discharge to/from a rheumatologist/orthopedist/radiologist within 180 days before the first diagnosis.
** Statin initiators below the 5th and noninitiators above the 95th percentile before propensity score matching.
†† First hand OA diagnosis shifted to 180 days prior to the first recorded diagnosis.

diseases. After PS matching, covariate balance was achieved across all included covariates with a postmatching C statistic of C = 0.55 (Table 1). Censoring due to change in exposure status was comparable (censoring reasons before and after PS matching are shown in Supplement 8, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract).

We observed HRs around the null for hand OA in statin initiators when compared to noninitiators in all PS-matched analyses (overall HR 0.98 [95% CI 0.88–1.09]) (Table 2). Multivariable adjusted analyses were similar to PS-matched results. Comparing statin initiators to initiators of glaucoma therapy yielded a slightly decreased but nonsignificant HR of 0.85 (95% CI 0.56–1.29). The comparison of medium- or high-dose initiators versus low-dose initiators yielded a nonsignificant HR of 1.02 (95% CI 0.85–1.21) (Table 2). Subgroup analyses are shown in Supplement 9 (available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract).

The outcome of generalized OA was not associated with statin initiation in the overall PS-matched cohort (HR 1.10 [95% CI 0.99–1.21]), or in any subgroup (see Supplement 10, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract). The results for all negative control outcomes were null overall and in subgroups (Figure 3 and Supplement 11, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract). We observed significantly increased HRs for myopathy in association with statin initiation, particularly during early treatment, whereas HRs for composite cardiovascular outcomes decreased with increasing duration of statin use (Table 3). In the sensitivity analysis without a run-in period we observed a decreasing HR for hand OA with decreasing duration of statin use (see Supplement 12, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract), which was the same for negative control outcomes (an example of peptic ulcer is shown in Supplement 13, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract).

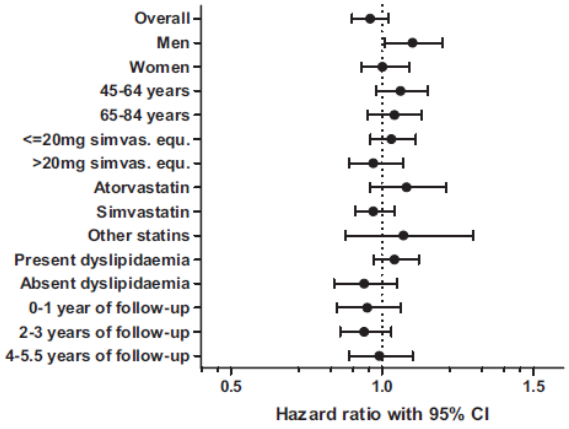

Figure 3. Forest plots of the association of statin initiation and incident psoriasis overall and in subgroups in the propensity score (PS)–matched cohort. PS matching occurred on the basis of all covariates (Table 1), except for hip fracture and fluoroquinolone antibiotics. Additionally, nonsteroidal antiinflammatory drugs, family history of psoriasis, and history of organ transplantation were introduced into PS matching. simvas = simvastatin; equ = equivalent; 95% CI = 95% confidence interval.

HRs for hand OA in statin initiators and noninitiators within deciles of the PS were heterogeneous in the lowest quantiles, probably due to the low number of outcomes in the initiator group (1–3 outcomes per quantile), but resolved after asymmetric trimming (see Supplement 14, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23616/abstract).

DISCUSSION

In this large retrospective cohort study, we did not find any evidence of a protective effect of statins on the risk of developing hand OA, irrespective of sex, age, statin dose, individual statin, preexisting dyslipidemia, or treatment duration. Based on our database analysis, we are not able to rule out effects of statins on osteoarthritic tissue, as previously observed in preclinical studies (6–8). However, our data suggest that even if such effects are present, they do not translate into a clinically meaningful reduced risk of hand OA in patients receiving statin therapy.

Direct comparison of our results to previous observational studies on the association of statin initiation and the risk of OA is difficult due to heterogeneous methods (9–12). However, consistent with the study by Valdes et al (14), we observed no association between statin initiation and hand OA, but we could not confirm the 23% decreased risk of generalized OA in association with statin use. Valdes et al included 2,366 OA patients (605 patients with generalized OA) and 805 controls from secondary care in a cross-sectional study (14). Detailed clinical information allowed accurate identification of generalized OA, based on radiographic assessment, but statin use was captured as a crude dichotomous variable, with limited control of confounding factors (14). The fact that we consistently observed increased crude HRs for the association between statin initiation and generalized OA highlights the need to adequately control for confounding. Furthermore, radiographic OA and symptomatic OA do not necessarily overlap, since the prevalence of radiographic OA is usually much higher than the prevalence of symptomatic OA (37).

Our results contradict findings from the only previous CPRD-based observational cohort study, which investigated the association between statin use and incident OA of any joint among 4,976 statin users and 11,633 nonusers. The authors of that study reported a strongly increased risk of OA (odds ratio [OR] 2.55 [95% CI 2.3–2.9]) among low-dose statin users (n = 1,109) when compared to nonusers (10), whereas the subgroup of statin users receiving a daily dosage of ≥18.5 mg/day (n = 1,298) revealed a significantly decreased OR of 0.41 (95% CI 0.3–0.5) (10). The subgroup of low-dose statin users had a calculated daily dosage below the usual minimum dosage applied in clinical practice (0.01–4.6 mg of simvastatin equivalents), but the methodology in that study insufficiently described how dosage calculations were made. Differences in the observed

Table 3. Association of statin initiation and incident positive control outcomes overall and by duration of follow-up (no run-in period applied for the outcome myopathy)*

	Before propensity score matching				Propensity score matched		
	Time, statin initiators + noninitiators†	Events	Crude HR (95% CI)	Adjusted HR (95% CI)‡	Time, statin initiators + noninitiators†	Events	Matched HR (95% CI)‡
Major CV events/death	1,177.4 + 29,687.1	146,573	1.49 (1.46–1.53)	0.87 (0.85–0.89)	1,153.8 + 1,122.1	16,626	0.89 (0.87–0.92)
Duration of follow-up, years							
0–1	309.5 + 7,354.8	34,863	1.75 (1.68–1.83)	1.06 (1.02–1.11)	3,03.9 + 315.1	4,718	1.01 (0.96–1.07)
2–3	467.8 + 11,900.5	57,436	1.41 (1.36–1.46)	0.82 (0.78–0.85)	4,58.6 + 462.7	6,456	0.84 (0.80–0.88)
4–5.5	400.1 + 10,431.8	54,274	1.41 (1.36–1.47)	0.79 (0.76–0.82)	3,91.3 + 344.3	5,452	0.86 (0.82–0.91)
Myopathy overall	1,385.9 + 32,433.6	126,380	3.08 (3.03–3.13)	2.32 (2.28–2.37)	1,350.9 + 1,517.6	21,906	2.11 (2.06–2.17)
Duration of follow-up, years							
0–1.5	5,25.8 + 10,835.0	42,948	4.38 (4.28–4.49)	3.35 (3.25–3.45)	5,14.2 + 562.3	10,153	2.90 (2.77–3.03)
>1.5–3.5	4,64.8 + 11,502.7	43,982	2.49 (2.41–2.58)	1.85 (1.78–1.92)	452.8 + 548.7	6,711	1.71 (1.63–1.79)
>3.5–6	3,95.3 + 10,095.8	39,450	2.20 (2.12–2.29)	1.63 (1.56–1.70)	383.8 + 406.7	5,042	1.59 (1.50–1.68)

* HR = hazard ratio; 95% CI = 95% confidence interval; CV = cardiovascular.
† Observation time in 1,000 person-years.
‡ Adjusted for, and propensity score–matched with, all covariates (Table 1), except for hip fracture and fluoroquinolone antibiotics.

risks when compared to our study may partly be explained by different outcome definitions (i.e., "OA in any joint" versus hand OA in our study) (10). We previously observed that "OA in any joint" mainly refers to OA in weight-bearing joints (hip and knee) in CPRD data (data not shown). Lifestyle factors, such as physical activity, occupation, or body mass index, are important risk factors for OA in weight-bearing joints but are not sufficiently captured in the CPRD. Thus, the risk of confounding is high when assessing OA in weight-bearing joints in CPRD data (38). Two previous CPRD-based case–control studies demonstrated differing results when studying OA in weight-bearing and non–weight-bearing joints. One study demonstrated a decreased risk of total hip or knee arthroplasty in patients with type 2 DM, whereas the other study showed no association between type 2 DM and hand OA (39,40). The authors of the former study hypothesized that their finding is likely explained by confounding (40). This hypothesis is supported by a recently published cohort study, which was based on 4 homogeneous prospective cohorts from Sweden and showed no association between statin use and OA, after adjusting for various life style factors and physical activity (41).

Results remained unchanged in a sensitivity analysis in which we required patients to have at least 1 year of statin-free history on the database instead of 3 years (data not shown). Furthermore, we observed unchanged results in a sensitivity analysis, in which we did not include use of other lipid-lowering agents in the PS model, suggesting that potential confounding due to antiinflammatory properties of drugs such as fibrates (42,43) was not an issue. The lack of a suitable active comparator group is known to impose several challenges when studying statins in large electronic databases, because noninitiators may inherently differ from statin initiators in ways that are not captured electronically. For example, maintenance of statin therapy positively correlates with increased health care utilization and positive health-related behavior (22), whereas frailty and comorbidities predict decreased statin adherence (21). Furthermore, nonadherence is not possible in nonusers, which can lead to differential censoring.

To address these challenges, we introduced a series of additional analyses to control for residual confounding by health care utilization (surveillance bias) and differential censoring. First, in a sensitivity analysis without a run-in period, the risk of hand OA decreased with decreasing duration of statin use. The fact that we observed the same trend of decreasing risks with decreasing duration of statin use for all negative control outcomes suggests that this result does not reflect a true drug effect, but rather surveillance bias in poor statin adherers, who may also be less likely to seek medical attention in case of occurrence of new symptoms (21). Thus, previous results of negative associations between statin use and OA not applying a run-in period might have been biased (9–12,14). Second, observed null results throughout the PS-matched cohort with various negative control outcomes suggest that surveillance bias does not play a major role after applying a run-in period. Third, we observed a nonsignificant result when comparing the risk of hand OA between statin initiators and initiators of glaucoma therapy. Given the 15% decreased point estimate and limited power in this analysis, surveillance bias cannot be entirely ruled out (26,28). However, the null result when comparing medium- or high-dose statin initiators to low-dose statin initiators suggests no dose-dependent protective effect of statins on hand OA after also controlling for surveillance bias. Fourth, the validity of our study population was corroborated by the observed previously known associations between the positive control outcomes and statin exposure, as shown in pivotal randomized controlled trials (33,34,44). Finally, the fact that our results of the multivariate and PS-matched analyses were similar further supports the robustness of our methodology.

Despite the rigorous methodology of this study, our results must be interpreted in the context of the following limitations. First, hand OA is a straightforward diagnosis, mostly made in primary care without diagnostic testing or secondary care referrals (45). Therefore, we were not able to perform a formal validation of the hand OA outcome using diagnoses made in secondary care. The fact, however, that results remained virtually unchanged in a sensitivity analysis with a stricter outcome definition (11.6% of outcomes) suggests that outcome misclassification did not explain our result. Second, hand OA records in the CPRD likely do not reflect exact disease onset in all cases, since hand OA is a non–life-threatening disease of gradual onset. However, a shift of the onset diagnosis by 180 days did not meaningfully change results. Third, we did not include a robust estimator in our model due to computational power restrictions, although patients may have entered our cohort multiple times. However, inclusion of a robust variance estimator in overall analysis of hand OA in all statin initiators widened the 95% CIs by a maximum of 0.01. Fourth, prematching and postmatching C statistics showed strongly increasing covariate balance with increasing levels of restriction of the study population, with almost perfect balance (of measured covariates) after PS matching, supporting our decision to apply the chosen restrictions and PS matching. Given the strict inclusion criteria of PS matching applied in our study, our final study population is not population-based but highly restricted to maximize comparability between study groups. We therefore refrained from presenting incidence rates of hand OA, since these rates would not be generalizable to the general population. Finally, despite rigorous PS matching, we could not control for unmeasured confounding by physical impact on finger joints, genetic predisposition, menopause, and long-term cholesterol deposition, since these parameters are not recorded in the CPRD and may have led to residual confounding (3,38,46,47).

Despite these limitations, this is to our knowledge the largest observational study evaluating the risk of hand OA in association with statin initiation, using a well-validated primary care database and robust analytical methods. In conclusion, our results suggest no effect of statins on the risk of hand OA, irrespective of sex, age, statin dose, statin agent, preexisting dyslipidemia, or treatment duration. Additional analyses, including a comparison with an active comparator as well as several negative control outcomes, corroborate this finding.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Meier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Burkard, Bloechliger, Spoendlin.
Acquisition of data. Jick, Meier.
Analysis and interpretation of data. Burkard, Hügle, Layton, Glynn, Bloechliger, Frey, Jick, Meier, Spoendlin.

ADDITIONAL DISCLOSURE

Dr. Layton is an employee of RTI International, which performs contract work for government and commercial clients, including pharmaceutical companies.

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Supp1. Exclusion criteria: conditions associated with secondary osteoarthritis or differential diagnosis of HOA any time before cohort entry[1,2,3]

- a record of a previous finger injury (e.g. fracture, dislocation, tear of ligament, or finger amputation)
- a recorded finger malformation/misalignment
- hypermobility syndrome
- hyperparathyroidism
- acromegaly
- disorder of iron metabolism (haemochromatosis)
- inflammatory polyarthropathies (rheumatoid arthritis, Psoriatic and enteropathic arthropathies, Juvenile arthritis, gout, crystal arthropathies, other arthropathies/arthritis)
- haem – or hydrarthrosis
- Wilson disease

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Supp2. Topical glaucoma therapy – exposure definition

Topical glaucoma therapy contained sympathomimetics, parasympathomimetics, carbonic anhydrase inhibitors, betablockers, prostaglandine-analogues and others such as guanethidine and dapiprazole.

Supp3. Read code list of the primary outcome HOA

N050100 Generalised osteoarthritis of the hand
N051400 Localised; primary osteoarthritis of the hand
N053400 Localised osteoarthritis; unspecified; of the hand
N054400 Oligoarticular osteoarthritis; unspecified; of hand
N05z400 Osteoarthritis NOS; of the hand
N05zF00 Osteoarthritis NOS; of MCP joint
N05zG00 Osteoarthritis NOS; of PIP joint of finger
N05zH00 Osteoarthritis NOS; of DIP joint of finger
N05z411 Finger osteoarthritis NOS
N052400 Localised; secondary osteoarthritis of the hand
2G26.00 O/E - hands - Heberden's nodes
N050111 Heberdens' nodes
N050700 Heberden's nodes with arthropathy
N050112 Bouchards' nodes
N050300 Bouchard's nodes with arthropathy

Supp4. Read code list of the secondary outcome GOA

N050.00 Generalised osteoarthritis - OA
N050000 Generalised osteoarthritis of unspecified site
N050200 Generalised osteoarthritis of multiple sites
N050400 Primary generalized osteoarthrosis
N050z00 Generalised osteoarthritis NOS

Supp5. Characteristics of statin initiators and non-initiators before the application of exclusion criteria

	Statin init (N=1,044,573)	Non-init. (N=33,219,405)
Mean age in years (SD*)	63.6 (12.7)	36.8 (22.5)
Mean no. of GP contacts ≤1 yr before cohort entry‡ (SD*)	18.7 (14.5)	8.8 (10.5)
Female	482,687 (46.2%)	17,909,707 (46.2%)
Current smoker	224,329 (21.5%)	6,898,976 (20.1%)
Average alcohol intake (>14 units/week)	118,087 (11.3%)	2,086,987 (6.3%)
Comorbidities before cohort entry:		
Obesity (BMI>30kg/m^2)	307,828 (29.5%)	4,200,729 (12.7%)
Osteoporosis**	47,117 (4.5%)	471,877 (1.4%)
Dyslipidaemia‡	654,631 (62.7%)	3,282,731 (9.9%)
Angina pectoris	124,133 (11.9%)	379,347 (1.1%)
Type2 diabetes	180,060 (17.2%)	356,089 (1.1%)

Hypertension	495,921 (47.5%)	3,034,683 (9.1%)
Chronic ischaemic heart dis.	136,485 (13.1%)	347,494 (1.1%)
Congestive heart failure	35,565 (3.4%)	209,641 (0.6%)
Hypothyroidism	73,316 (7.0%)	785,717 (2.4%)
Vascular disease	51,412 (4.9%)	340,834 (1.0%)
Chronic kidney disease (stage≥3)	73,417 (7.0%)	405,352 (1.2%)
Hip fracture	13,683 (1.3%)	218,880 (0.7%)
Liver disease	9209 (0.9%)	93,812 (0.3%)
Macular degeneration	14,478 (1.4%)	133,037 (0.4%)
COPD	45,325 (4.3%)	356,886 (1.1%)
Anaemia	68,910 (6.6%)	1,439.924 (4.3%)
Pressure ulcer/decubitus	11,523 (1.1%)	142,160 (0.4%)
Deep vein thrombosis	23,267 (2.2%)	239,356 (0.7%)
Dysphagia	19,109 (1.8%)	230,343 (0.7%)
≥1 hospitalization ≤1 year before the cohort entry	205,741 (19.7%)	3,615,894 (10.9%)
Incontinence	28,337 (2.7%)	430,366 (1.3%)
Pneumonia	33,144 (3.2%)	632,333 (1.9%)
Psychotherapy‡	51,093 (4.9%)	1,285,608 (3.9%)
Delusional disorders	9659 (0.9%)	171,661 (0.5%)
Co-medication ≤180 days before cohort entry:		
Hormone replacement therapy	45,027 (4.3%)	995,901 (3.0%)
Oral corticosteroids	46,501 (4.5%)	693,165 (2.1%)
Opioids	77,210 (7.4%)	973,679 (2.9%)
Fluoroquinolone antibiotics	12,842 (1.2%)	205,056 (0.6%)
Benzodiazepines	71,542 (6.9%)	1,113,104 (3.4%)
COPD drugs‡	15,201 (1.5%)	142,232 (0.4%)
Coronary vasodilators	90,411 (8.7%)	238,074 (0.7%)
Histamin-2 antagonists	31,925 (3.1%)	430,164 (1.3%)
SSRIs	62,338 (6.0%)	1,336,583 (4.0%)
Other lipid-lowering agents	19,369 (1.9%)	65,683 (0.2%)
Number of CV drugs†: 0	386,471 (37.0%)	29,299,671 (88.2%)
Number of CV drugs†: 1-3	500,555 (47.9%)	3,372,725 (10.2%)
Number of CV drugs†: 4-12	157,547 (15.1%)	547,009 (1.7%)

Supplementary Tab1. Characteristics of statin initiators and non-initiators before the application of exclusion criteria

*SD: standard deviation

**defined as an osteoporosis diagnose or intake of drugs affecting bone metabolism

‡only records on separate days

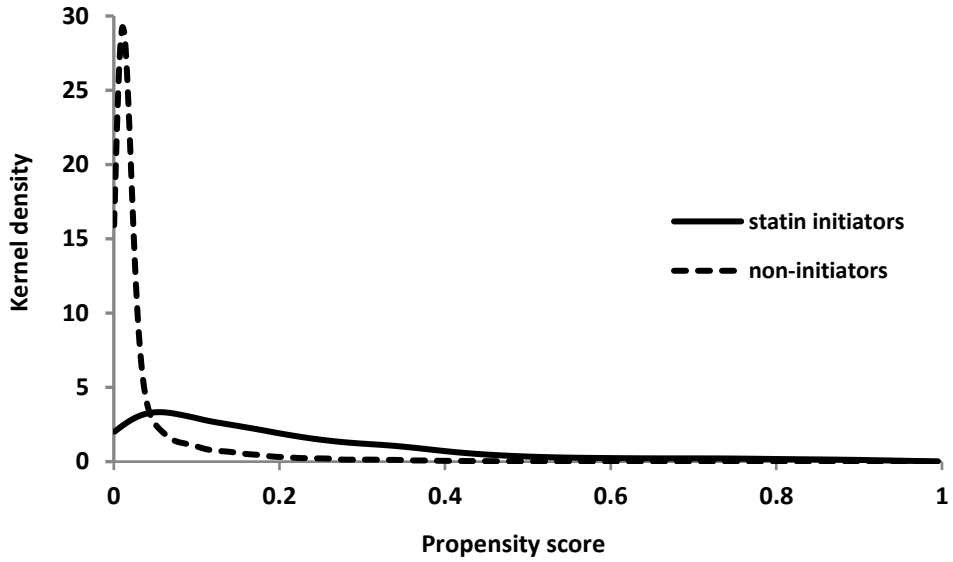
ŧdefined as either an hyperlipidaemia Read code, a laboratory value of low density lipoprotein >3 mmol/l, of high density lipoprotein <1 mmol/l, or of triglycerides >1.7 mmol/l

Łas a proxy for psychiatric disease

Ŧdefined as xanthines, long-acting inhaled anticholinergics including combinations, indacaterol, or aclidinium including combinations

†defined as ACE-inhibitors, ATII-inhibitors, beta-blockers, calcium-channel-blockers, diuretics, thrombocyte-aggregation-inhibitors, vitamin K antagonists, acetylsalicylic acid, other lipid-lowering agents, insulin, oral antidiabetics, or antiarrhythmics

Supp6. PS distribution in statin initiators and non-initiators before PS-matching



Supp7. Characteristics of statin initiators before application of exclusion criteria and after exclusion criteria were applied (both before PS-matching)

	Statin init after exclusion criteria (N=237,864)	Statin init before exclusion criteria (N=1,044,573)
Mean age in years (SD*)	62.7 (9.4%)	63.6 (12.7)
Mean no. of GP contacts ≤1 yr before cohort entry‡ (SD*)	18.6 (11.9%)	18.7 (14.5)
Female	116,938 (49.2%)	482,687 (46.2%)
Current smoker	47,940 (20.2%)	224,329 (21.5%)
Average alcohol intake (>14 units/week)	24,347 (10.2%)	118,087 (11.3%)
Comorbidities before cohort entry:		
Obesity (BMI>30kg/m^2)	69,683 (29.3%)	307,828 (29.5%)
Osteoporosis**	7567 (3.2%)	47,117 (4.5%)
Dyslipidaemia‡	173,648 (73.0%)	654,631 (62.7%)
Angina pectoris	20,416 (8.6%)	124,133 (11.9%)
Type2 diabetes	42,980 (18.1%)	180,060 (17.2%)
Hypertension	119,142 (50.1%)	495,921 (47.5%)
Chronic ischaemic heart dis.	17,219 (7.2%)	136,485 (13.1%)
Congestive heart failure	3981 (1.7%)	35,565 (3.4%)
Hypothyroidism	16,480 (6.9%)	73,316 (7.0%)
Vascular disease	9139 (3.8%)	51,412 (4.9%)
Chronic kidney disease (stage≥3)	11,696 (4.9%)	73,417 (7.0%)
Hip fracture	1629 (0.7%)	13,683 (1.3%)
Liver disease	1218 (0.5%)	9209 (0.9%)
Macular degeneration	1870 (0.8%)	14,478 (1.4%)
COPD	7900 (3.3%)	45,325 (4.3%)
Anaemia	12,614 (5.3%)	68,910 (6.6%)
Pressure ulcer/decubitus	1902 (0.8%)	11,523 (1.1%)
Deep vein thrombosis	3680 (1.6%)	23,267 (2.2%)

Dysphagia	3607 (1.5%)	19,109 (1.8%)
≥1 hospitalization ≤1 year before the cohort entry	37,127 (15.6%)	205,741 (19.7%)
Incontinence	4934 (2.1%)	28,337 (2.7%)
Pneumonia	5930 (2.5%)	33,144 (3.2%)
Psychotherapyŧ	10,288 (4.3%)	51,093 (4.9%)
Delusional disorders	2069 (0.9%)	9659 (0.9%)
Co-medication ≤180 days before cohort entry:		
Hormone replacement therapy	14,660 (6.2%)	45,027 (4.3%)
Oral corticosteroids	8695 (3.7%)	46,501 (4.5%)
Opioids	12,756 (5.4%)	77,210 (7.4%)
Fluoroquinolone antibiotics	2648 (1.1%)	12,842 (1.2%)
Benzodiazepines	13,676 (5.8%)	71,542 (6.9%)
COPD drugsŀ	3156 (1.3%)	15,201 (1.5%)
Coronary vasodilators	17,928 (7.5%)	90,411 (8.7%)
Histamin-2 antagonists	6527 (2.7%)	31,925 (3.1%)
SSRIs	13,751 (5.8%)	62,338 (6.0%)
Other lipid-lowering agents	4408 (1.9%)	19,369 (1.9%)
Number of CV drugs†: 0	76,455 (32.1%)	386,471 (37.0%)
Number of CV drugs†: 1-3	127,690 (53.7%)	500,555 (47.9%)
Number of CV drugs†: 4-12	33,719 (14.2%)	157,547 (15.1%)

Supplementary Tab2. Characteristics of statin initiators before application of exclusion criteria and after exclusion criteria were applied (both before PS-matching)

*SD: standard deviation

**defined as an osteoporosis diagnose or intake of drugs affecting bone metabolism

‡only records on separate days

ŧdefined as either an hyperlipidaemia Read code, a laboratory value of low density lipoprotein >3 mmol/l, of high density lipoprotein <1 mmol/l, or of triglycerides >1.7 mmol/l

Łas a proxy for psychiatric disease

ŀdefined as xanthines, long-acting inhaled anticholinergics including combinations, indacaterol, or aclidinium including combinations

†defined as ACE-inhibitors, ATII-inhibitors, beta-blockers, calcium-channel-blockers, diuretics, thrombocyte-aggregation-inhibitors, vitamin K antagonists, acetylsalicylic acid, other lipid-lowering agen

Supp8. Censoring reasons before and after PS-matching

	Before PS-matching		PS-matched	
	Statin init.	**Non-init.**	**Statin init.**	**Non-init.**
Osteoarthritis	14,285 (6.0%)	286,867 (4.8%)	13,924 (6.0%)	13,216 (5.7%)
Rheumatoid arthritis, other arthropathies/arthritis	2825 (1.2%)	70,962 (1.2%)	2761 (1.2%)	2754 (1.2%)
Crystal arthropathies	72 (0.0%)	1245 (0.0%)	71 (0.0%)	67 (0.0%)
Disorders of iron metabolism	67 (0.0%)	1715 (0.0%)	66 (0.0%)	90 (0.0%)
Gout	4076 (1.7%)	53,946 (0.9%)	3973 (1.7%)	3648 (1.6%)
Haem – or hydrarthoris	36 (0.0%)	727 (0.0%)	35 (0.0%)	34 (0.0%)
Hyperparathyroidism	267 (0.1%)	3720 (0.1%)	262 (0.1%)	221 (0.1%)
Wilson disease, acromegaly or hypermobility syndrome	17 (0.0%)	520 (0.0%)	17 (0.0%)	13 (0.0%)
Previous finger injury	663 (0.3%)	20,629 (0.3%)	651 (0.3%)	623 (0.3%)
Finger malformation/misalignment	1768 (0.7%)	31,869 (0.5%)	1711 (0.7%)	1401 (0.6%)
Amputation of at least wrist level	34 (0.0%)	610 (0.0%)	34 (0.0%)	18 (0.0%)
Cancer except non-melanoma skin cancer	10,436 (4.4%)	220,305 (3.7%)	10,182 (4.4%)	10,613 (4.5%)

HIV/AIDS	8 (0.0%)	393 (0.0%)	8 (0.0%)	7 (0.0%)
Alcoholism / substance abuse	4764 (2.0%)	89,733 (1.5%)	4671 (2.0%)	3738 (1.6%)
Prescription for cerivastatin	341 (0.1%)	5370 (0.1%)	339 (0.2%)	312 (0.1%)
Change of exposure status	53,887 (22.7%)	608,577 (10.1%)	53,032 (22.7%)	57,035 (24.4%)
Loss to follow-up	63,984 (26.9%)	2,192,617 (36.4%)	63,455 (27.2%)	75,098 (32.2%)
Completed follow-up, end of the study period	77,190 (32.5%)	2,352,102 (39.1%)	75,371 (32.3%)	59,758 (25.6%)
Death	2412 (1.0%)	60,056 (1.0%)	2324 (1.0%)	4251 (1.8%)

Supplementary Tab3. Censoring criteria frequencies before and after PS-matching

Supp9. Results of the association of dose-dependent statin initiation (>20mg simvastatin equivalent initiation [medium or high-dose] versus ≤20 mg simvastatin equivalent initiation [low-dose]) and incident HOA overall and in subgroups

	Before PS-matching				PS-matched		
	Obs.-time* in medium/high-dose init. + low-dose init.	HOA Events	HR crude (95% CI)	HR adjusted† (95% CI)	Obs.-time* in medium/high-dose init. + low-dose init.	HOA Events	HR matched† (95% CI)
Overall	301.3+ 467.1	734	1.17 (1.01-1.35)	1.16 (1.00-1.35)	240.1+ 236.9	498	1.02 (0.85-1.21)
Sex							
Men	163.9+ 228.1	225	1.03 (0.79-1.35)	1.01 (0.77-1.32)	121.6+ 120.4	145	0.95 (0.69-1.32)
Women	137.4+ 239.1	509	1.32 (1.11-1.57)	1.24 (1.04-1.48)	117.4+ 115.8	343	1.06 (0.86-1.31)
Age in years							
45-64	190.1+ 256.7	452	1.17 (0.97-1.41)	1.20 (0.99-1.45)	143.7+ 140.1	320	1.09 (0.88-1.36)
65-84	111.3+ 210.4	282	1.13 (0.88-1.43)	1.09 (0.85-1.39)	95.8+ 95.5	180	1.02 (0.76-1.36)
Agent							
Atorvastatin	60.1+ 116.2	150	1.26 (0.91-1.75)	1.25 (0.89-1.74)	53.5+ 52.3	89	1.05 (0.69-1.59)
Simvastatin	228.2+ 303.0	533	1.12 (0.94-1.33)	1.13 (0.95-1.34)	167.4+ 167.5	361	1.05 (0.86-1.29)
other	13.0+ 47.9	51	1.13 (0.59-2.16)	1.10 (0.57-2.14)	10.4+ 9.7	14	1.24 (0.43-3.57)
Indication for statin initiation							
Present dyslip.	555.5+ 3638.3	4328	1.02 (0.93-1.11)	1.10 (1.00-1.20)	536.9+ 513.5	1106	1.01 (0.89-1.13)
Absent dyslip.	69.0+ 144.1	150	1.16 (0.83-1.62)	1.14 (0.81-1.61)	54.4+ 53.9	78	1.16 (0.74-1.80)
Duration of follow-up							
0–1 year	87.0+ 122.4	178	1.07 (0.80-1.44)	1.04 (0.77-1.40)	66.7+ 66.2	117	0.79 (0.55-1.14)
2–3 years	123.0+ 184.8	288	1.27 (1.01-1.60)	1.29 (1.02-1.63)	97.0+ 94.8	207	1.13 (0.86-1.49)
4–5.5 years	91.3+ 160.0	268	1.21 (0.88-1.43)	1.12 (0.87-1.43)	76.4+ 75.9	174	1.06 (0.79-1.43)

Supplementary Tab4. Results of the association of dose-dependent statin initiation and incident HOA overall and in subgroups

*Observation-time in 1000 person-years

†Adjusted for / PS-matched with all covariates (table1), except for hip fracture and fluoroquinolone antibiotics. Additionally adjusted for non-steroidal anti-inflammatory drugs, non-melanoma skin cancer, and family history of cataract

Supp10. Results of the association of statin initiation and incident GOA overall and in subgroups

	Before PS-matching				PS-matched		
	Obs.-time* in statin init. + non-init.	GOA events	HR crude (95% CI)	HR adjusted† (95% CI)	Obs.-time* in statin init. + non-init.	GOA events	HR matched† (95% CI)
Overall	807.7+ 22,838.9	15,377	1.56 (1.46-1.68)	1.15 (1.07-1.25)	791.2+ 763.0	1471	1.10 (0.99-1.21)
Sex							
Men	407.0+ 9337.5	3734	1.57 (1.38-1.79)	1.09 (0.94-1.25)	399.8+ 376.6	418	1.18 (0.98-1.44)
Women	400.7+ 13,501.4	11,643	1.72 (1.58-1.88)	1.18 (1.08-1.29)	388.5+ 385.5	1036	1.11 (0.98-1.25)
Age in years							
45-64	466.2+ 17,340.2	9189	1.61 (1.45-1.78)	1.14 (1.02-1.28)	452.3+ 448.1	698	1.08 (0.93-1.26)
65-84	341.5+ 5498.7	6188	1.19 (1.08-1.31)	1.18 (1.06-1.31)	333.7+ 312.0	790	1.02 (0.88-1.17)
Daily dose in simvastatin equivalents							
≤20mg	492.1+ 22,838.9	15,075	1.59 (1.46-1.74)	1.14 (1.04-1.26)	489.9+ 462.2	941	1.06 (0.94-1.21)
>20mg	315.5+ 22,838.9	14,876	1.52 (1.35-1.70)	1.16 (1.03-1.30)	315.3+ 310.9	569	1.11 (0.94-1.31)
Agent							
Atorvastatin	186.2+ 22,838.9	14,792	1.84 (1.61-2.10)	1.34 (1.17-1.54)	186.0+ 171.4	393	1.14 (0.94-1.40)
Simvastatin	557.1+ 22,838.9	15,079	1.43 (1.31-1.56)	1.05 (0.96-1.16)	555.2+ 540.3	989	1.00 (0.88-1.13)
other	64.4+ 22,838.9	14,654	1.95 (1.56-2.43)	1.37 (1.10-1.71)	64.3+ 61.5	147	1.14 (0.82-1.58)
Indication for statin initiation							
Present dyslip.	584.3+ 3780.6	3157	1.39 (1.26-1.52)	1.15 (1.05-1.27)	564.9+ 535.2	1027	1.06 (0.94-1.20)
Absent dyslip.	223.4+ 19,058.4	12,220	1.73 (1.53-1.97)	1.17 (1.03-1.34)	223.1+ 222.7	468	1.06 (0.88-1.27)
Duration of follow-up							
0–1 year	212.9+ 5678.8	3262	1.74 (1.51-2.01)	1.20 (1.03-1.40)	209.0+ 216.1	382	1.05 (0.86-1.28)
2–3 years	321.3+ 9163.8	5999	1.58 (1.41-1.77)	1.20 (1.06-1.35)	314.9+ 315.4	585	1.13 (0.96-1.33)
4–5.5 years	273.5+ 7996.3	6116	1.45 (1.28-1.63)	1.09 (0.96-1.24)	267.3+ 231.5	504	1.09 (0.92-1.31)

Supplementary Tab5. Results of the association of statin initiation and incident GOA overall and in subgroups

*Observation-time in 1000 person-years

†Adjusted for / PS-matched with all covariates (table1), except for hip fracture.

Supp11. Results of the association of statin initiation and incident negative control outcomes overall and in subgroups

	Before PS-matching				PS-matched		
	Obs.-time* in statin init. + non-init.	Cataract events	HR crude (95% CI)	HR adjusted† (95% CI)	Obs.-time* in statin init. + non-init.	Cataract events	HR matched† (95% CI)
Overall	1104.7+ 27,859.1	75,129	2.30 (2.24-2.36)	1.17 (1.14-1.20)	1079.9+ 1042.1	11,590	1.02 (0.98-1.06)
Sex							
Men	551.0+ 11,474.4	25,563	2.30 (2.21-2.39)	1.22 (1.17-1.28)	541.1+ 507.7	4576	1.06 (1.00-1.13)
Women	553.6+ 16,384.7	49,566	2.41 (2.33-2.49)	1.14 (1.10-1.18)	536.7+ 533.2	6981	1.00 (0.95-1.04)
Age in years							
45-64	621.4+ 20,579.3	19,083	2.63 (2.49-2.78)	1.09 (1.03-1.16)	602.0+ 593.8	2469	1.11 (1.02-1.20)
65-84	483.2+ 7279.8	56,046	1.42 (1.38-1.47)	1.17 (1.13-1.21)	472.2+ 446.3	8790	1.06 (1.02-1.11)
Daily dose in simvastatin equivalents							
≤20mg	664.9+ 27,859.1	72,780	2.36 (2.29-2.44)	1.16 (1.12-1.20)	661.7+ 623.1	7266	1.04 (1.00-1.09)
>20mg	439.8+ 27,859.1	71,247	2.20 (2.11-2.29)	1.17 (1.13-1.23)	439.7+ 433.4	4740	0.96 (0.91-1.02)
Agent							
Atorvastatin	256.0+ 27,859.1	70,317	2.25 (2.14-2.37)	1.18 (1.12-1.24)	255.9+ 234.7	2593	1.08 (1.00-1.16)
Simvastatin	760.0+ 27,859.1	73,289	2.36 (2.28-2.43)	1.18 (1.15-1.22)	757.7+ 737.3	8479	1.02 (0.98-1.07)
Other statins	88.6+ 27,859.1	69,319	1.92 (1.74-2.11)	1.00 (0.91-1.10)	88.6+ 84.5	830	0.96 (0.84-1.10)
Indication for statin initiation							
Present dyslip.	809.0+ 4942.8	22,437	1.54 (1.49-1.59)	1.16 (1.12-1.20)	779.8+ 738.1	8098	1.07 (1.02-1.12)
Absent dyslip.	295.7+ 22,916.4	52,692	2.54 (2.42-2.66)	1.27 (1.21-1.34)	295.5+ 295.2	3402	0.94 (0.88-1.00)
Duration of follow-up							
0–1 years	292.0+ 6943.6	15,112	2.26 (2.14-2.39)	1.18 (1.11-1.25)	286.1+ 295.8	2640	0.98 (0.90-1.05)
2–3 years	440.2+ 11,192.7	28,659	2.23 (2.14-2.33)	1.14 (1.09-1.19)	430.4+ 430.9	4439	0.99 (0.93-1.05)
4–5.5 years	372.5+ 9722.8	31,358	2.37 (2.28-2.47)	1.21 (1.15-1.26)	363.3+ 315.4	4511	1.08 (1.02-1.15)

Supplementary Tab6. Results of the association of statin initiation and incident cataract overall and in subgroups

*Obs.-time in 1000 person-years

†Adjusted for / PS-matched with all covariates (table1), except for hip fracture and fluoroquinolone antibiotics. Additionally adjusted for non-steroidal anti-inflammatory drugs, non-melanoma skin cancer, and family history of cataract

	Before PS-matching				PS-matched		
	Obs.-time* in statin init. + non-init.	**Peptic ulcer events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs.-time* in statin init. + non-init.**	**Peptic ulcer events**	**HR matched† (95% CI)**
Overall	1179.6+ 28,871.6	38,633	1.62 (1.56-1.69)	1.03 (0.98-1.08)	1154.8+ 1111.6	4562	1.00 (0.94-1.06)
Sex							
Men	570.9+ 11,628.0	17,485	1.46 (1.38-1.55)	0.99 (0.93-1.05)	561.0+ 526.5	2271	0.95 (0.88-1.03)
Women	608.8+ 17,243.6	21,148	1.75 (1.65-1.85)	1.07 (1.01-1.14)	591.4+ 583.1	2220	1.10 (1.01-1.19)
Age in years							
45-64	632.8+ 20,800.9	17,812	1.72 (1.61-1.84)	1.02 (0.94-1.10)	613.2+ 604.3	1649	1.04 (0.95-1.15)
65-84	546.8+ 8070.7	20,821	1.16 (1.10-1.22)	1.02 (0.97-1.08)	535.2+ 503.5	2853	0.98 (0.91-1.06)
Daily dose in simvastatin equivalents							
≤20mg	714.4+ 28,871.6	37,782	1.73 (1.64-1.82)	1.05 (1.00-1.11)	711.7+ 667.7	3037	0.96 (0.90-1.04)
>20mg	465.2+ 28,871.6	37,085	1.46 (1.36-1.56)	0.98 (0.92-1.05)	465.1+ 457.7	1665	1.03 (0.93-1.13)
Agent							
Atorvastatin	273.0+ 28,871.6	36,846	1.79 (1.65-1.93)	1.11 (1.02-1.20)	272.9+ 249.2	1164	1.00 (0.89-1.13)
Simvastatin	812.6+ 28,871.6	37,816	1.55 (1.48-1.63)	1.00 (0.95-1.05)	810.9+ 788.2	3128	0.99 (0.92-1.06)
Other statins	94.0+ 28,871.6	36,439	1.74 (1.51-1.99)	1.01 (0.88-1.17)	94.0+ 89.4	450	0.80 (0.66-0.96)
Indication for statin initiation							
Present dyslip.	863.4+ 5196.0	7814	1.52 (1.44-1.60)	1.02 (0.96-1.08)	834.0+ 788.7	2949	0.96 (0.90-1.04)
Absent dyslip.	316.2+ 23,675.6	30,819	2.05 (1.91-2.19)	1.03 (0.96-1.11)	316.0+ 315.5	1599	1.04 (0.95-1.15)
Duration of follow-up							
0–1 years	305.9+ 7134.8	9448	1.73 (1.60-1.88)	1.17 (1.08-1.28)	300.1+ 310.4	1271	1.03 (0.92-1.15)
2–3 years	467.8+ 11,575.2	15,288	1.53 (1.43-1.63)	0.98 (0.91-1.05)	458.1+ 458.1	1798	0.93 (0.85-1.02)
4–5.5 years	405.9+ 10,161.6	13,897	1.65 (1.54-1.77)	0.98 (0.91-1.06)	396.5+ 343.1	1493	1.07 (0.96-1.18)

Supplementary Tab7. Results of the association of statin initiation and incident peptic ulcer overall and in subgroups

*Obs.-time in 1000 person-years

†Adjusted for / PS-matched with all covariates (table1), except for hip fracture and fluoroquinolone antibiotics. Additionally adjusted for non-steroidal anti-inflammatory drugs, and proton pump inhibitor initiation

	Before PS-matching				PS-matched		
	Obs.-time* in statin init. + non-init.	**Psor. events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs.-time* in statin init. + non-init.**	**Psor. events**	**HR matched† (95% CI)**
Overall	1186.2+ 28,856.4	51,722	1.18 (1.13-1.23)	1.00 (0.96-1.05)	1113.4+ 1076.5	4450	0.96 (0.90-1.02)
Sex							
Men	580.0+ 11,755.6	21,402	1.15 (1.09-1.22)	1.02 (0.95-1.09)	570.7+ 534.3	2101	1.10 (1.01-1.20)
Women	606.2+ 17,100.9	30,320	1.20 (1.14-1.27)	0.99 (0.93-1.06)	588.6+ 582.1	2375	1.00 (0.93-1.09)
Age in years							
45-64	629.7+ 20,626.3	37,901	1.25 (1.19-1.32)	1.00 (0.95-1.06)	610.4+ 601.2	2598	1.06 (0.98-1.15)
65-84	556.5+ 8230.1	13,821	1.15 (1.08-1.23)	1.01 (0.94-1.08)	545.1+ 511.2	1866	1.04 (0.95-1.13)
Daily dose in simvastatin equivalents							
≤20mg	719.1+ 28,856.4	50,827	1.22 (1.16-1.28)	1.06 (1.00-1.12)	716.6+ 671.7	2863	1.03 (0.96-1.11)
>20mg	467.1+ 28,856.4	50,226	1.12 (1.05-1.20)	0.92 (0.86-0.99)	466.9+ 458.6	1802	0.97 (0.89-1.07)
Agent							
Atorvastatin	274.9+ 28,856.4	49,930	1.28 (1.18-1.38)	1.08 (0.99-1.17)	274.8+ 250.2	1110	1.08 (0.96-1.21)
Simvastatin	816.2+ 28,856.4	50,906	1.13 (1.07-1.19)	0.96 (0.91-1.01)	814.4+ 789.7	3153	0.97 (0.91-1.04)
other	95.1+ 28,856.4	49,548	1.34 (1.17-1.53)	1.14 (1.00-1.31)	95.0+ 90.2	410	1.07 (0.88-1.30)
Indication for statin initiation							
Present dyslip.	863.7+ 5153.1	11,672	1.09 (1.04-1.14)	1.03 (0.98-1.09)	834.2+ 787.7	3281	1.04 (0.97-1.12)
Absent dyslip.	322.4+ 23,703.3	40,050	1.12 (1.03-1.21)	0.99 (0.91-1.07)	322.3+ 320.6	1230	0.94 (0.84-1.05)
Duration of follow-up							
0–1 years	307.5+ 7132.6	12,877	1.25 (1.15-1.35)	1.01 (0.93-1.10)	290.6+ 301.0	1289	0.95 (0.85-1.06)
2–3 years	470.4+ 11,569.1	20,654	1.19 (1.11-1.27)	1.00 (0.93-1.07)	442.0+ 444.4	1796	0.94 (0.86-1.03)
4–5.5 years	408.3+ 10,154.7	18,191	1.12 (1.04-1.21)	1.02 (0.94-1.11)	380.9+ 331.1	1365	0.99 (0.89-1.10)

Supplementary Tab8. Results of the association of statin initiation and incident psoriasis overall and in subgroups

*Obs.-time in 1000 person-years

† Adjusted for / PS-matched with all covariates (table1), except for hip fracture and fluoroquinolone antibiotics. Additionally adjusted for non-steroidal anti-inflammatory drugs, family history of psoriasis and history of organ transplantation

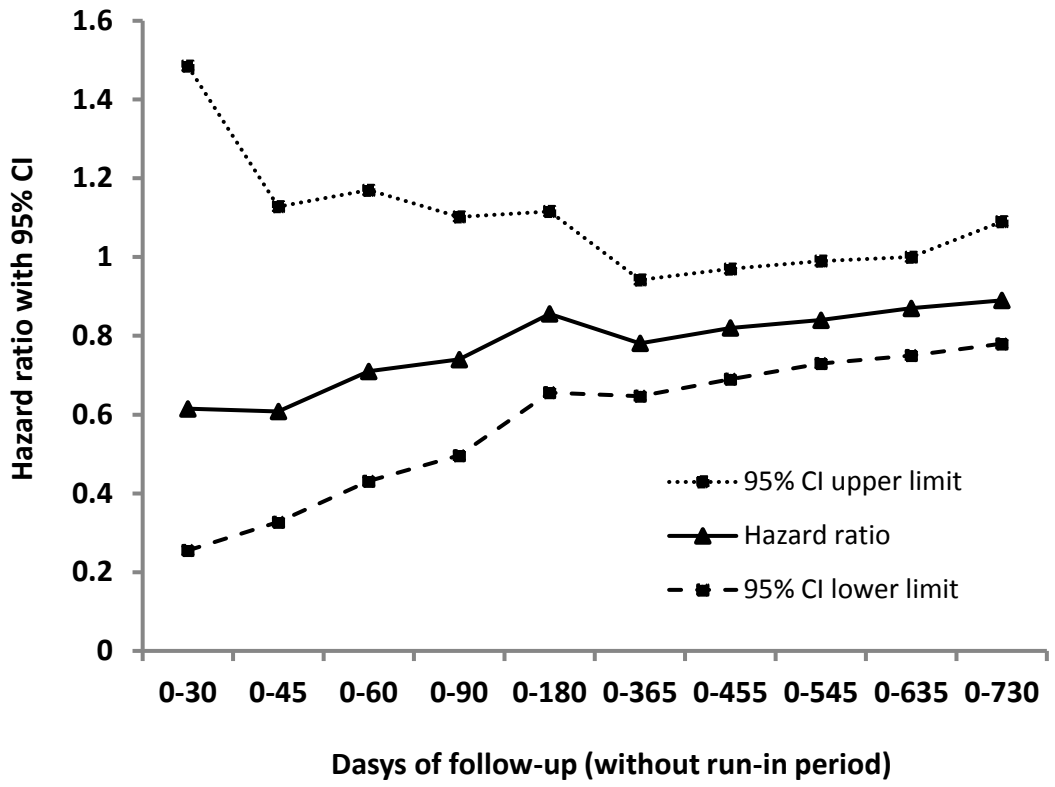
	Before PS-matching				PS-matched		
	Obs.-time* in statin init. + non-init.	**Tinnitus events**	**HR crude (95% CI)**	**HR adjusted† (95% CI)**	**Obs.-time* in statin init. + non-init.**	**Tinnitus events**	**HR matched† (95% CI)**
Overall	1172.5+ 28,608.2	107,367	1.16 (1.13-1.19)	1.01 (0.98-1.05)	1147.8+ 1102.6	9361	1.00 (0.96-1.04)
Sex							
Men	572.3+ 11,649.9	47,132	1.14 (1.10-1.19)	1.04 (1.00-1.08)	562.7+ 526.2	4750	1.01 (0.95-1.07)
Women	600.2+ 16,958.4	60,235	1.16 (1.11-1.21)	0.99 (0.95-1.03)	582.6+ 573.9	4682	0.95 (0.90-1.00)
Age in years							
45-64	626.7+ 20,542.8	78,485	1.20 (1.16-1.25)	1.00 (0.96-1.05)	606.4+ 596.7	5361	0.99 (0.94-1.04)
65-84	545,8+ 8065.4	28,882	1.16 (1.11-1.21)	1.05 (1.00-1.11)	535.0+ 502.2	3953	1.02 (0.96-1.08)
Daily dose in simvastatin equivalents							
≤20mg	711.1+ 28,608.2	105,396	1.14 (1.10-1.18)	1.01 (0.98-1.06)	708.3+ 662.5	5575	1.01 (0.96-1.06)
>20mg	461.4+ 28,608.2	104,471	1.20 (1.14-1.25)	1.10 (1.05-1.15)	461.3+ 461.2	3839	1.06 (0.99-1.13)
Agent							
Atorvastatin	272.7+ 28,608.2	103,605	1.13 (1.07-1.20)	1.00 (0.95-1.07)	272.6+ 249.0	2040	1.08 (0.99-1.18)
Simvastatin	805.3+ 28,608.2	105,872	1.17 (1.13-1.21)	1.02 (0.98-1.05)	803.5+ 778.5	6607	1.01 (0.96-1.06)
other	94.5+ 28,608.2	102,890	1.15 (1.04-1.27)	1.01 (0.92-1.12)	94.5+ 89.8	770	0.97 (0.85-1.12)
Indication for statin initiation							
Present dyslip.	853.2+ 5067.7	25,630	1.00 (0.97-1.04)	1.04 (1.00-1.07)	823.3+ 777.2	6928	1.02 (0.97-1.07)
Absent dyslip.	319.3+ 23,540.5	81,737	1.07 (1.01-1.13)	1.01 (0.95-1.07)	319.1+ 318.8	2364	0.96 (0.89-1.04)
Duration of follow-up							
0–1 years	304.9+ 7091.9	25,781	1.22 (1.16-1.29)	1.01 (0.96-1.08)	299.2+ 309.2	2570	1.00 (0.92-1.08)
2–3 years	465.4+ 11,478.6	42,588	1.17 (1.12-1.23)	1.03 (0.98-1.08)	455.7+ 455.2	3809	0.99 (0.93-1.05)
4–5.5 years	402.2+ 10,037.7	38,998	1.10 (1.05-1.16)	1.01 (0.96-1.07)	392.9+ 338.1	2982	1.02 (0.95-1.09)

Supplementary Tab9. Results of the association of statin initiation and incident tinnitus overall and in subgroups

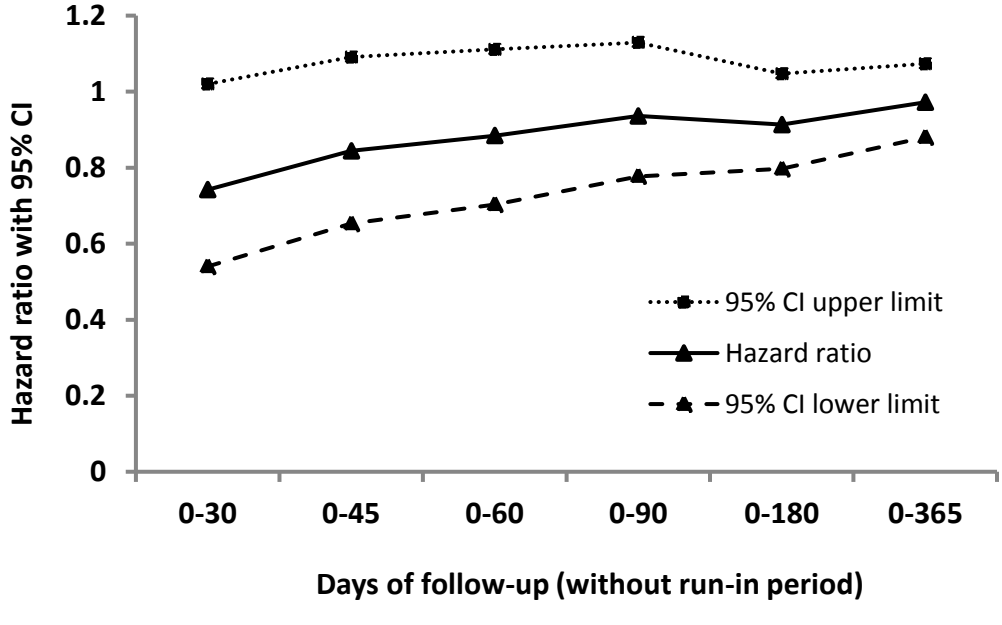
*Obs.-time in 1000 person-years

† Adjusted for / PS-matched with all covariates (table1), except for hip fracture, fluoroquinolone antibiotics, and selective serotonin re-uptake inhibitors. Additionally adjusted for non-steroidal anti-inflammatory drugs, and initiation anti-depressant drugs

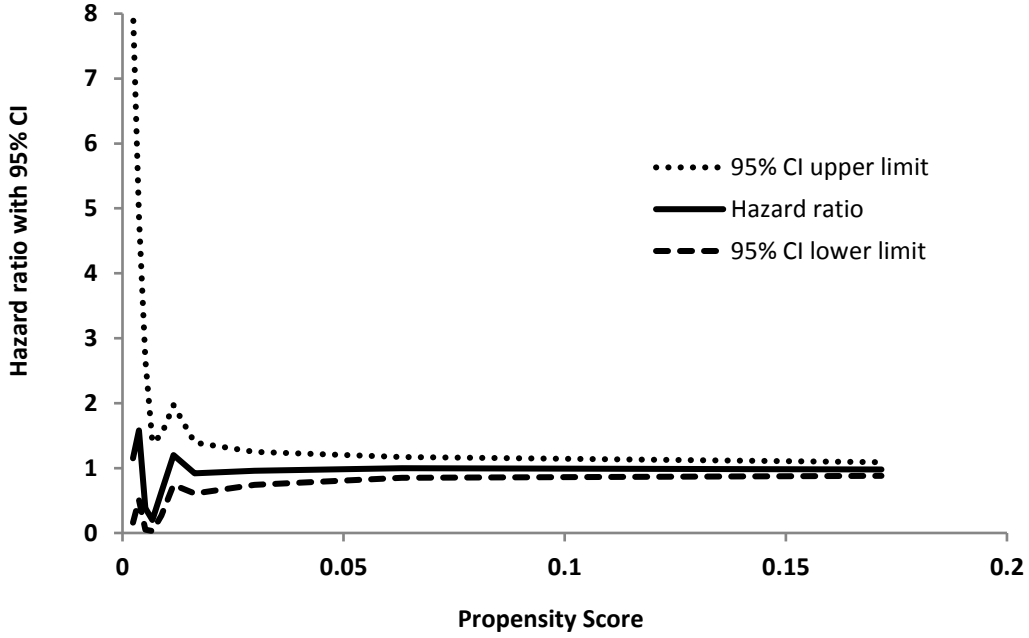
Supp12. Hazard ratios for HOA in statin initiators within certain follow-up periods compared to non-initiators



Supp13. Hazard ratio for peptic ulcer in statin initiators within certain follow-up periods compard to non-initiators



Supp14. HRs of HOA in statin initiators and non-initiators within deciles of the PS



8.9 Appendix 9

Supplementary Table6. Baseline characteristics of statin initiators and non-initiators (follow-up >180 days) with information on index of multiple deprivation only before and after propensity score-matching

	Before PS-matching		PS-matched	
	Statin initiators (N=39,572)	Non-initiators (N=1,707,695)	Statin initiators (N=37,881)	Non-initiators (N=37,881)
Mean age in years (SD)	56.4 (5.3)	53.1 (5.6)	56.3 (5.4)	56.5 (5.3)
Mean follow-up in years (SD)	3.2 (2.1)	3.8 (1.9)	3.2 (2.1)	3.3 (1.9)
Mean number of GP contacts ≤1 year before cohort entry* (SD)	18.9 (11.8)	9.6 (9.4)	18.5 (11.5)	18.8 (13.3)
Current smokers	9053 (22.9%)	330,572 (19.4%)	8648 (22.8%)	8548 (22.6%)
Average alcohol intake (>14 units/week)	1364 (3.5%)	55,369 (3.2%)	1332 (3.5%)	1357 (3.6%)
IMD quintile 1 (least deprived)	8605 (21.8%)	469,821 (27.5%)	8353 (22.1%)	8202 (21.7%)
IMD quintile 2	9184 (23.2%)	432,993 (25.4%)	8837 (23.3%)	8832 (23.3%)
IMD quintile 3	7962 (20.1%)	355,278 (20.8%)	7593 (20.0%)	7969 (21.0%)
IMD quintile 4	7799 (19.7%)	274,582 (16.1%)	7411 (19.6%)	7457 (19.7%)
IMD quintile 5	6022 (15.2%)	175,021 (10.3%)	5687 (15.0%)	5421 (14.3%)
Comorbidities before cohort entry:				
Obesity (BMI>30kg/m^2)	14,992 (37.9%)	325,260 (19.1%)	13,964 (36.9%)	13,944 (36.8%)
Osteoporosis†	994 (2.5%)	29,947 (1.8%)	963 (2.5%)	1032 (2.7%)
Dyslipidemia‡	30,640 (77.4%)	307,155 (18.0%)	28,981 (76.5%)	30,183 (79.7%)
Angina pectoris	2006 (5.1%)	11,954 (0.7%)	1761 (4.7%)	1479 (3.9%)
Type2 diabetes	7557 (19.1%)	15,916 (0.9%)	6194 (16.4%)	5273 (13.9%)
Hypertension	18,617 (47.1%)	229,735 (13.5%)	17,556 (46.4%)	18,189 (48.0%)
Ischemic heart disease	1427 (3.6%)	3976 (0.2%)	1215 (3.2%)	926 (2.4%)
Congestive heart failure	233 (0.6%)	1532 (0.1%)	206 (0.5%)	169 (0.5%)
Hypothyroidism	4298 (10.9%)	97,908 (5.7%)	4060 (10.7%)	4321 (11.4%)
Vascular disease	969 (2.5%)	21,045 (1.2%)	910 (2.4%)	875 (2.3%)
Chronic kidney disease	1044 (2.6%)	9247 (0.5%)	1009 (2.7%)	975 (2.6%)
Hip fracture	107 (0.3%)	4493 (0.3%)	102 (0.3%)	107 (0.3%)
Liver disease	275 (0.7%)	3973 (0.2%)	259 (0.7%)	249 (0.7%)
COPD‡	844 (2.1%)	15,488 (0.9%)	793 (2.1%)	796 (2.1%)
Deep vein thrombosis	601 (1.5%)	16,456 (1.0%)	571 (1.5%)	592 (1.6%)
Dysphagia	628 (1.6%)	17,779 (1.0%)	989 (1.7%)	1079 (1.8%)
≥1 hospitalization ≤1 year before cohort entry (SD)	6100 (15.4%)	150,766 (8.8%)	5797 (15.3%)	5955 (15.7%)
Incontinence	1291 (3.3%)	34,656 (2.0%)	1214 (3.2%)	1284 (3.4%)
Pneumonia	838 (2.1%)	33,597 (2.0%)	803 (2.1%)	801 (2.1%)
Psychotherapy§	2442 (6.2%)	79,361 (4.7%)	2335 (6.2%)	2442 (6.5%)
Co-medication ≤180 days before cohort entry:				
Hormone replacement therapy	7016 (17.7%)	300,738 (17.6%)	6766 (17.9%)	7069 (18.7%)
Oral corticosteroids	1619 (4.1%)	41,219 (2.4%)	1538 (4.1%)	1579 (4.2%)
Opioids	2472 (6.3%)	51,189 (3.0%)	2328 (6.2%)	2260 (6.0%)
Benzodiazepines	2482 (6.3%)	70,956 (4.2%)	2368 (6.3%)	2456 (6.5%)
COPD‖ drugs	405 (1.0%)	7313 (0.4%)	380 (1.0%)	346 (0.9%)
Coronary vasodilators	1846 (4.7%)	4360 (0.3%)	1550 (4.1%)	1176 (3.1%)
Histamin-2 antagonists	960 (2.4%)	21,715 (1.3%)	898 (2.4%)	904 (2.4%)
SSRIs	3701 (9.4%)	103,470 (6.1%)	3522 (9.3%)	3578 (9.5%)
Other lipid lowering agents	658 (1.7%)	2946 (0.2%)	607 (1.6%)	546 (1.4%)
Number of CV drugs¶: 0	14,399 (36.4%)	1,453,157 (85.1%)	14,392 (38.0%)	14,812 (39.1%)

Number of CV drugs¶: 1-3	21,448 (54.2%)	242,661 (14.2%)	20,430 (53.9%)	19,848 (52.4%)
Number of CV drugs¶: 4-12	3725 (9.4%)	11,877 (0.7%)	3059 (8.1%)	3221 (8.5%)

SD: standard deviation, GP: general practitioner, IMD: index of multiple deprivation, COPD: chronic obstructive pulmonary disease, SSRI: serotonin reuptake inhibitor, CV: cardiovascular PS: propensity score

* only records on separate days

† defined as an osteoporosis diagnose or intake of drugs affecting bone metabolism

‡ defined as either an hyperlipidemia Read code, a laboratory value of low density lipoprotein >3 mmol/l, of high density lipoprotein <1 mmol/l, or of triglycerides >1.7 mmol/l

§ as a proxy for psychiatric disease

ll defined as xanthines, long-acting inhaled anticholinergics including combinations, indacaterol, or aclidinium including combinations

¶ defined as ACE-inhibitors, ATII-inhibitors, beta-blockers, calcium-channel-blockers, diuretics, thrombocyte-aggregation-inhibitors, vitamin K antagonists, acetylsalicylic acid, other lipid lowering agents, insulin, oral antidiabetics, or antiarrhythmics