PROFESSOR LARS VEDEL KESSING (Orcid ID : 0000-0001-9377-9436)

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New drug candidates for depression – A nation-wide population-based study

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Lars Vedel Kessing, professor, MD, DMSc*
Helene Charlotte Rytgaard, MSc**
Thomas Alexander Gerds, professor, MSc., PhD**
Michael Berk, professor, MD, PhD***
Claus Thorn Ekstrøm, professor, MSc, PhD**
Per Kragh Andersen, professor, MSc PhD, DMSc**

Psychiatric Center Copenhagen, Rigshospitalet, University of Copenhagen, Denmark*
Department of Biostatistics, University of Copenhagen, Denmark**
School of Medicine, Deakin University, Australia***
Orygen, The National Centre of Excellence in Youth Mental Health, the Department of Psychiatry, and the Florey Institute for Neuroscience and Mental Health, University of Melbourne, Australia***

Correspondence to:
Lars Vedel Kessing, Psychiatric Center Copenhagen, Department O, 6233
Blegdamsvej 9, 2100 Copenhagen, Denmark
and University of Copenhagen, Faculty of Health and Medical Sciences
Tel.: 45 - 38 64 70 81;
Mail: lars.vedel.kessing@regionh.dk

ABSTRACT (word count: 199)

Objective: To investigate whether continued use of non-aspirin NSAID, low dose aspirin, high dose aspirin, statins, allopurinol, and angiotensin agents decreases the rate of incident depression using Danish nation-wide population-based registers.

Methods: All persons in Denmark who purchased the exposure medications of interest between 1995 and 2015 and a random sample of 30 % of the Danish population were included in the study. Two different outcome measures were included, 1) a diagnosis of depressive disorder at a psychiatric hospital as inpatient or outpatient and 2) a combined measure of a diagnosis of depression or use of antidepressants.

Results: A total of 1,576,253 subjects were exposed to one of the six drugs of interest during the exposure period from 2005 to 2015. Continued use of low dose aspirin, statins, allopurinol, and angiotensin agents were associated with a decreased rate of incident depression according to both outcome measures. Continued uses of non-aspirin NSAIDs as well as high dose aspirin were associated with an increased rate of incident depression.

Conclusion: The findings support the potential of agents acting on inflammation and the stress response system in depression as well as the potential of population-based registers to systematically identify drugs with repurposing potential.

Key words: drug repurposing, NSAID, aspirin, statins, allopurinol, angiotensin, inflammation, stress, depressive disorder, antidepressants

Significant outcomes

- Initial use of all exposure drugs was associated with increased rates of incident depression reflecting positive associations between the physical illnesses for which the drugs were prescribed and depression.
- Compared to initial use, continued treatments with low dose aspirin, statins, allopurinol, and angiotensin agents may decrease the rate of incident depression whereas continued treatments with non-aspirin NSAIDs as well as high dose aspirin may not.
- These findings are in accordance with pathophysiological mechanisms of action of the drugs.

Limitations

- Although we addressed confounding in the design of the study analyses and by adjusting for comorbid physical illnesses confounding factors cannot be excluded.

Introduction

Depression imposes a very high societal burden in terms of cost, lost productivity, morbidity, suffering, and mortality [1], and is a leading cause of disability and disease burden worldwide [2]. Despite the high prevalence and healthcare costs of depression, the inefficient, costly and unpredictable drug development process has led to decreased public and investor confidence in the abilities of companies to develop safe and efficacious drugs [3, 4]. One of the major reasons for this decrease is the long and costly development from preclinical to clinical trials as a major proportion of

candidate drugs fails to reach the market due to disappointing efficacy or unpredictable side effects in humans [3]. There has also been an industry focus on monoamine targets leading to many similar agents, but few truly novel ones.

An increasingly prevalent idea in many fields of medicine – such as oncology – is drug repurposing [4, 5]. This refers to a process whereby a clinically-used drug is shown to possess hitherto-unknown potential utility in an alternative disorder. Repurposing assumes that the agent is safe and that use can be expanded safely at usually low cost in a novel niche [4, 6]. Indeed, much drug use in psychiatry at present is off-label.

We systematically used Danish nation-wide population-based registers to investigate whether agents with an *a-priori* preclinical or theoretical evidence base may have effects in depression. This approach is predicated on a theoretical construct, that of a shared pathway of risk for diverse non-communicable disorders, that include depression, cardiovascular disorders and diabetes. These disorders share common environmental risks as well as common biological pathways [7]. We studied 6 medications listed below, each with putative anti-inflammatory or neuroprotective effects.

Non-aspirin non-steroidal anti-inflammatory drugs (non-aspirin NSAID)

Depression has been associated with increased low grade inflammation as indicated by increased C-reactive protein (CRP) and cytokine levels [8-11]. A meta-analysis of randomized clinical trials suggested that treatment with NSAID decreases depressive symptoms without increased risks of adverse effects, however results were limited by small sample sizes, a high risk of bias and high heterogeneity across studies [12].

Aspirin

Aspirin inhibits cyclooxygenase-1 (COX-1) and acetylates COX-2, blocking the conversion of arachidonic acid to prostaglandins and thromboxane A2 [13]. Low dose of aspirin (75 mg to 150 mg / day) preferentially inhibits COX-1 while at higher doses ($\geq$ 500 mg / day) it additionally reduces COX-2 function. Preclinical evidence suggests that inhibition of COX-1 is neuroprotective whereas inhibition of COX-2 increases leukocyte recruitment into the brain exacerbating tissue damage [13]. An

epidemiological study reported that aspirin was associated with decreased risk of incident depression at a trend level during a median follow-up of seven years [14]. Subsequent studies have not confirmed that aspirin use was associated with decreased risk of incident depression [15-17]. In a pilot RCT in depression, aspirin demonstrated utility together with sertraline [18], and in bipolar depression, there was a tentative signal of the effects of combined aspirin and minocycline [19]. No study has specifically investigated associations between low versus high dose aspirin, respectively, and incident depression.

A total of 137 participants (mean age 65 y, 55.5% female) were using aspirin at base-

Statins

Statins may have effects in depression due to their anti-inflammatory functions [20, 21]. A meta-analysis including 7 randomized controlled trials found no overall effect differences on psychological wellbeing between statins and placebo but statins were associated with improvements in mood scores among patients with clinical depression [20, 21]. Accordingly, it was shown in a Swedish a register linkage study that statins might protect against depression [22].

Allopurinol

There is some evidence of dysregulation of the purinergic system in mood disorders. Blunted adenosine A2A receptor signalling is documented in depression [23], and there is provisional clinical evidence that allopurinol may have an efficacy signal in mania [24, 25]. There are no randomized clinical trials on allopurinol and depression.

Angiotensin agents

Based on the Wellcome Trust Case-Control Consortium genome-wide study angiotensin agents may have effects in mood disorders [26]. A number of observations have linked angiotensin converting enzyme polymorphisms with depression and the serotonine and dopamine neurotransmitter systems [27]. In a recent case-control study including 961 individuals we confirmed ACE inhibitors to be associated with a reduced likelihood for depression onset [28]. There are no randomized clinical trials on angiotensin agents and depression although there is a positive study of telmisartan in schizophrenia [29].

Aims of the study

We aimed to use Danish population-based registers to investigate whether the abovementioned drugs are associated with decreased risk of incident depression. To take into account confounding by indication we estimated the rate of incident depression during successive prescription periods of the drugs whereas the period with non-use was included for comparison.

We hypothesised that continued use of non-aspirin NSAID, low dose aspirin, statins, allopurinol, and angiotensin converting enzyme inhibitors and angiotensin antagonists (angiotensin agents) decreases the rate of incident depression, and that the rates decrease with the number of prescriptions.

Methods

The registers

Data were obtained by linking Danish population-based registers using the unique personal identification number, which is assigned to all 5.7 million persons living in Denmark, thus ensuring accurate linkage of information between registers, irrespective of changes in name and demographics [30]. In this way, the Medicinal Product Statistics [31] was linked with the Danish Medical Register on Vital Statistics [32], the Danish National Hospital Register [33] and the Danish Psychiatric Central Register [34].

The Medicinal Product Statistics contains data on all prescribed medication purchased at pharmacies from January 1, 1995 and onwards [31]. The register includes prescription data from all physicians in Denmark, i.e., from primary care including general practise and private specialists and from secondary outpatient hospital care settings. Non-aspirin NSAIDs, statins, angiotensin agents and allopurinol are available only by prescription, apart from low-dose ibuprofen, which is obtainable over-the-counter in Denmark (but as regular users of low-dose ibuprofen receive a 50% refund when redeeming a prescription for ibuprofen, thus most regular users of low-dose ibuprofen are also recorded in the database). Around 88 % of the total use of non-aspirin NSAIDs is by prescription and thus recorded in the register [35, 36]. Low-dose aspirin is primarily used for prevention and treatment of cardiovascular and thromboembolic events, with a daily recommended dose of 75–150 mg. Due to the reimbursement of 50 % of the cost, the vast majority (92 %) of the total sales of low-dose aspirin are

prescriptions, whereas high-dose aspirin (500 mg tablets), typically used for transient pain relief, is sold primarily over-the-counter in Denmark [37].

The Danish Medical Register on Vital Statistics [32] contains data on deaths.

The Danish National Hospital Register [33] contains data on all patients treated at all somatic hospitals as in- or outpatients in Denmark from 1 January 1977 and onwards as a part of the official Danish health survey [38]. Likewise, all psychiatric admissions and diagnoses are recorded in the register (as part of the Danish Psychiatric Central Register [34]) from 1 April 1970 and onwards. Since 1 January 1994 the ICD-10 has been in use in both registers [38] and since 1 January 1995 diagnoses from outpatient contacts have been included.

Diagnoses from primary care are not included in the registers but pharmacological treatment from primary care is recorded in the Danish Medical Register on Vital Statistics (as prescriptions from all other physicians).

Study population

All persons who purchased the exposure medications of interest at least once in the study period from January 1, 1995 to December 31, 2015 were identified in the Medicinal Product Statistics and entered into the study at the date of the first prescription. Additionally, a random sample consisting of 30 % of the Danish population was identified in the Danish Medical Register on Vital Statistics among all inhabitants in Denmark who were alive at January 1, 1995. The random sample included subjects who never bought the drug and thereby defines the group of unexposed subjects.

Exclusion criteria

The following individuals were excluded: individuals who purchased antidepressants at least once before the entry into the study (i.e., before a purchase of the current candidate drug) and individuals with a diagnosis of depression (back to 1970) prior to entry into the study.

Outcome

The primary outcome was a diagnosis of depressive disorder (ICD codes: DF32 - DF33.31) given at a psychiatric contact (as inpatients or outpatients) and as identified in the Danish Psychiatric Central Register. Secondary outcome was a combined endpoint of either the primary outcome or use of antidepressants (ATC: N06A).

Follow up period

Individuals were followed from entry into the study until date of death, date of a diagnosis of organic mental disorders, mental disorders due to psychoactive substance use, schizophrenia and mania/bipolar disorder (DF00-31.9 incl.) or December 31, 2015 (end of study period).

Exposure drugs

Low dose aspirin low-dose acetylsalicylic acid (ATC code B01AC06, 75 mg, 100 mg, or 150 mg per tablet), high dose aspirin (ATC code N02BA01, N02BA51, 500 mg tablets), non-aspirin NSAID (ATC code: M01AB15, M01AB55 and N02BE01), statins (HMG CoA reductase inhibitors, ATC codes: class C10AA), allopurinol (ATC codes: M04AA01, M04AA01, M04AA51) or angiotensin agents (angiotensin converting enzyme inhibitors and angiotensin antagonists, ATC codes: C09, C09C, C09D, C09X, C01CX06).

Comorbidity

Somatic diagnoses were categorised within nine ICD-8 and ICD-10 defined somatic disease chapters (I: infections, II: neoplasms, III: diseases of the blood, IV + IX +X: endocrine, nutritional and metabolic diseases and diseases of the circulatory or respiratory system, VI - VIII: Diseases of the nervous system, eye and ear, XI: diseases of the digestive system, XII: diseases of the skin and subcutaneous tissue, XIII: diseases of the musculoskeletal system, XIV: diseases of the genitourinary system and pregnancy, child birth and the puerperium) and separately within each of these disease areas.

Design of the analyses

There are two main potential sources of errors of the planned analyses that we needed to address: Confounding by indication may occur if an unobserved variable (e.g., some somatic comorbidity) is a risk factor for the studied outcome (depression) and at the same time is an indication of the drug of interest [39]. Detection bias may occur if subjects who are prescribed the drug of interest are more likely to get diagnosed with the outcome disease (depression) and/or to get antidepressants than unexposed subjects.

However, strategic sampling designs may be worked out, e.g., based on the self-controlled case series method [40] or as previously done in pharmaco-epidemiological studies by our group [41, 42] and this will under certain circumstances allow us to either completely eliminate or at least to assess the magnitude of the bias. To control for confounding effects and detection bias and to estimate the effect of duration of treatment, rates were compared during successive prescriptions of the exposure drugs as in prior studies [41, 42].

Statistical analyses

The association between drug exposure and the rate of incident depression was analysed separately for each candidate drug using Poisson regression. In these analyses, the principle is that each follow-up day where a subject is at risk for experiencing the outcome is categorized according to the *current values* of the drug exposure and of the potential confounders whereby the daily risk (the rate) of the outcome can be ascertained. The drug exposure on a given day during follow-up was defined as the cumulated number of prescriptions of the candidate drug during the last 10-years in appropriate categories (number and width of categories were chosen dependent on the general usage of the candidate drug). The category "1-2 prescriptions" was used as reference category in all analyses. The exposure category status was continuously updated during the follow up separately for each subject. To achieve the cumulation of exposure in the fixed 10-year period, all analyses of the outcomes were restricted to the calendar years 2005 to 2015 (the Danish Medical Product Statistics register starts in 1995). The analyses included all individuals who received any of the exposure drugs in Denmark from 2005 to 2015 together with all individuals who were part of the 30% random sample of the general population in 1995. Individuals of the 30% random sample were followed from 1 January 2005, the other individuals were followed from 1 January 2005 or first purchase of the candidate drug under study (whichever date came last). Follow-up continued until date of the event of interest, date of death, date of a diagnosis of organic mental disorders, mental disorders due to psychoactive substance use and schizophrenia (DF00-29 incl.) or 31 December 2015 (whichever date came first).

Note that an individual, initially selected as a member of the random sample of the population, may change exposure status if he or she later purchased the drug under study.

Separate analyses were performed to compare rates of incident depression among individuals exposed and unexposed to non-aspirin NSAIDs, low dose aspirin, high dose aspirin, statins, angiotensin agents and allopurinol (Table 2). Similarly, separate analyses were done with the combined endpoint (incident depression or use of antidepressants) as the outcome measure (Table 3).

All analyses were adjusted for gender, current age (0-17,18-21, 3-year intervals, 91-94, 95-99), current calendar year (1-year bands) and current employment status (working or student = reference, unemployed, age pension, disability, other). Additional analyses were performed in which we also adjusted for the time-dependent comorbidity status with additive effects of 9 dummy variables indicating the 9 comorbidity groups. The comorbidity status was always evaluated 10 years ago to avoid time-interference between exposure status and comorbidity.

Reported were hazard ratios with 95% confidence limits and exposure trend tests obtained with a likelihood ratio test comparing a Poisson regression model without candidate drug exposure to a model which assumes a linear increase in outcome hazard rate between the exposure categories (excluding the non-use category).

Data approval

The study was approved by the Data agency of the Capital Region of Denmark. Ethical approval of anonymous register studies are not needed according to Danish law.

Results

A total of 1,576,253 subjects were exposed to one of the six drugs of interest during the exposure period from 2005 to 2015. Table 1 shows the number of subjects exposed in total and for each drug (N), age and female gender proportion at first prescription.

Table 2 presents risk time in years with at least one prescription of the exposure drug, events with a diagnosis of depression (primary outcome), hazard ratios (HR) adjusted for age, gender, employment status, and calendar year (unadjusted and adjusted for somatic diagnoses) and trend tests. Table 3 presents similar analyses with a diagnosis of depression or use of antidepressants as the outcome measure (secondary outcome). For all drugs and in all analyses, the hazard rate of depression, and the hazard rate of depression or use of antidepressants, respectively, were significantly lower in subjects

with 0 prescriptions (non-use) compared with 1-2 prescriptions. Further, the hazard rates decreased with increasing number of prescriptions of low dose aspirin, statins, allopurinol, and angiotensin agents according to both outcome measures (for allopurinol the trend test was borderline statistically significant only in relation to a diagnosis of depression as outcome (Table 3)). Continued uses of non-aspirin NSAIDs as well as high dose aspirin were associated with increased rates of incident depression on both outcome measures.

Discussion

Using Danish nation-wide population-based registers we found that continued use of low dose aspirin, statins, allopurinol, and angiotensin agents were associated with a decreased rate of incident depression. HR of incident depression were systematically decreased early after prescription of all these drugs (HR for prescription period 3-9 versus prescription period 1-2 were below 1) and continued to decrease during at least one subsequent prescription period to a level below the rates during the unexposed periods. Continued uses of non-aspirin NSAIDs as well as high dose aspirin were associated with increased rate of incident depression.

It is not likely that these findings are a result of bias or confounding as one would expect that the rate of developing depression would in fact increase with the number of prescriptions and be higher among patients prescribed these drugs during longer time periods reflecting a stronger indication due to more comorbid severe physical disorder(s). In the pre-specified plan of analyses we decided to address bias or confounding by indication of the drug of interest in two different ways: First, by the design of the study as we decided to estimate the rate of depression during successive prescription periods of the drug compared with the rate during prescription period 1-2. We systematically confirmed in all analyses that the prescription period 1-2 was associated with increased HR of depression compared with the period with the non-use period (see Tables 1 and 2) illustrating confounding by indication since the drugs were prescribed for physical disorders associated with increased rate of developing depression including pain (NSAID [43]), osteoarthritis ([43] (NSAID), prevention and treatment of cardiovascular and thromboembolic events ([37] low-dose aspirin), arthritis urica ([44] allopurinol) and other kinds of arthritis ([44] NSAID), hypercholesterolemia ([45] statins) and hypertension ([46] angiotensin inhibitors) and congestive heart failure ([47

angiotensin inhibitors). Second, in addition to adjustments for gender, age, employment status and calendar period in 1-year periods, we adjusted the analyses for all physical comorbidities recorded in the Danish National Hospital Register as many patients suffer from multiple diseases (e.g. increased co-occurrence of chronic pain, depression and cardiovascular disease [48, 49]) and aiming to reduce unknown or residual confounding. Results from these analyses with adjustments for somatic diagnoses confirmed the results from primary analyses unadjusted for somatic illness. In addition, results from these analyses also confirmed confounding by indication as all HR rates for unexposed periods (prescription number 0) versus prescription period 1-2 were systematically higher in analyses adjusted for somatic diagnoses compared with analyses unadjusted for somatic diagnoses (Tables 1 and 2).

On the other hand, it cannot be excluded that the decrease in the risk of depression observed in patients taking more than 2 prescriptions is partly the result of better adherence to treatment in these patients with consequent better control of medical diseases and lower incidence of negative disease evolution and complications. Further, it's possible that low dose aspirin, statins, allopurinol and angiotensin agents are more likely to be used for prophylaxis in relatively asymptomatic people, whereas NSAID and high dose aspirin are more likely to be used for acute and chronic pain.

We confirmed our hypotheses regarding all the investigated drugs except continued use of non-aspirin NSAID. Further as suggested, high dose aspirin was associated with increased rates of incident depression potentially as at higher doses it might inhibit COX-2 increases leukocyte recruitment into the brain increasing tissue damage [13]. The non-aspirin NSAIDs may exert similar effects as these drugs are nonselective inhibitors of both COX-1 and COX-2 [50, 51]. Further, non-aspirin NSAIDS are primarily used for moderate to severe pain, and this indication is known to increase the risk of diverse mood and anxiety disorders [52]. We have no other methodological explanations as to why non-aspirin NSAIDs were associated with increased incidence of depression.

Other advantages of the study

First, the study included all persons in Denmark who purchased the exposure medication of interest (100%) together with a random sample of 30 % of the Danish population. Second, two different outcome measures were included, 1) a diagnosis of depressive disorder at a psychiatric hospital contact as inpatient or outpatient and 2) a combined

measure of a diagnosis of depression or use of antidepressants . Notably, the study includes prescription data from all physicians in Denmark, i.e., from primary care including general practise and private specialists and from secondary outpatient hospital care.

As can be seen from Tables 2 and 3, the number of events was substantially higher with outcome measure 2 than with outcome measure 1 but the results of analyses with the two outcome measures were very similar serving to increase the internal and external validity of the findings. Third, potential reverse causation is substantively excluded as only incident depression/use of antidepressants were included in the analyses since we excluded individuals who have got antidepressants (from 1995 to 2005) or a diagnosis of depression (back to 1970) prior to the drug class of interest. Fourth, the follow-up period included a 10 years period (from 2005 to 2015). Finally, as the first study ever we estimated associations with incident depression in relation to the duration of treatment during successive drug prescriptions.

Limitations

The primary outcome measure was not research-based but based on clinical diagnoses. However, the ICD-10 diagnosis of depression recorded in the Danish Psychiatric Central Research Register has a high validity as compared with a research diagnostic interview with the Clinical Assessment in Neuropsychiatry (SCAN [53].

Further, we added analyses with a combined outcome measure on a diagnosis of depression or the use of antidepressants and systematically confirmed results from the primary analyses. We did not include continued use of antidepressants as a separate outcome measure as such a measure is arbitrarily defined and as antidepressants are prescribed for other conditions than depression.

As depression is often undiagnosed or untreated, the increased HR of prescription period 1-2 versus period 0 is likely underestimated.

As with all other registers including nationwide medication data, the Danish Medicinal Product Statistics includes no information on adherence or dose of the exposure drugs, although repeat prescriptions are a reasonable proxy of adherence [31]. As we estimated the rate of incident depression during successive prescription periods it is unlikely that non-adherence substantially confounded our results.

Finally, it cannot be excluded that there may be a therapeutic window for some of the exposure drugs as HR for some drugs showed a tendency to decrease initially and increase during late prescription periods. For example, HR for statins show a drop of HR to 0.55-0.56 early on and then a rise up to 0.72 by the end (Table 3) and HR for allopurinol was around 1.0 in late prescription periods. However, caution should be exerted with such an interpretation as HR from late prescription periods were based on a short risk time and few events.

Perspectives

Considering the relatively weak evidence on antidepressant effects of the investigated drugs (as summarized in the introduction of the paper) it is surprising how consistent we were able to confirm our hypotheses using the present Danish population-based data. Population-based registers have not previously been used to systematically pursue drug repurposing and is not widely used as a method of identifying agents for re-purposing [5, 54]. As illustrated by the present study, population-based registers are of value to systematically identify drugs with repurposing potentials. Thus, these findings should be replicated in other population-based registers using similar designs and statistical analyses to address selection and confounding factors.

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Conflict of Interest Disclosure:

Potential conflicts of interest involving the work: none

Financial activities outside the work:

Lars Vedel Kessing has within the preceding three years been a consultant for Sunovion. Michael Berk has had interactions in the last 5 years with Janssen Cilag, Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Grunbiotics, LivaNova, Lundbeck, Merck, Mylan, Otsuka and Servier. Other authors report no financial activities.

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Access to Data and Data Analysis: LVK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HCR and TAG conducted and are responsible for the data analysis in cooperation with LVK, CTE and PKA. Table1. Number of individuals exposed in total and for each drug (N) during the exposure period 2005 to 2015, age (median, quartiles) and female gender proportion (%) at date of first prescription.

Drug	N	Age	Female proportion
Total	1576253	57 (43;69)	52.9
Non-aspirin NSAID	1016259	54 (38;69)	55.1
Low dose aspirin	315542	65 (56;74)	46.7
High dose aspirin	56189	58 (45;70)	62.3
Statins	497080	62 (53;70)	48.5
Allopurinol	50476	66 (55;76)	30.8
Angiotensin agents	494183	61 (52;71)	48.8

Table 2. Number of individuals with at least one prescription of the drug (N), risk time, events with a diagnosis of depression, hazard ratios (HR) of depression adjusted for age, sex, employment status, and calendar year (unadjusted and adjusted for somatic diagnoses).

Variable	Prescription number	Risk time (per 1000 person years)	Events with depression	Unadjusted for somatic diagnoses	Trend test	Adjusted for somatic diagnoses	Trend test
				Hazard ratio (95% CI)	p*	Hazard ratio (95% CI)	p*
Non-aspirin NSAIDs	1-2	5065	7664	1	1.08 (1.07-1.09) p < 0.001	1	1.07 (1.06-1.08) p < 0.001
	0	12229	14456	0.62 (0.60-0.64)		0.67 (0.65-0.69)	
	3-9	2331	4059	1.30 (1.25-1.36)		1.27 (1.22-1.32)	
	10-19	954	1668	1.31 (1.24-1.39)		1.26 (1.20-1.33)	
	20-29	478	872	1.37 (1.27-1.47)		1.31 (1.22-1.40)	
	30-39	296	578	1.47 (1.35-1.60)		1.40 (1.28-1.52)	
	40-49	197	375	1.43 (1.29-1.59)		1.36 (1.22-1.51)	
	> 50	474	1010	1.63 (1.53-1.75)		1.53 (1.43-1.64)	
Low dose Aspirin	1-2	1167	2058	1	0.67 (0.62-0.71)	1	0.93 (0.91-0.94)
	0	12478	16002	0.53 (0.51-0.56)		0.62 (0.59-0.65)	
	3-9	1301	1906	0.86 (0.81-0.92)		0.86 (0.81-0.91)	
	10-19	1326	1479	0.67 (0.62-0.71)		0.93 (0.91-0.94)	

	20-29	981	1079	0.66 (0.61-0.71)	p < 0.001	0.67 (0.62-0.72)	p < 0.001
	30-39	871	950	0.66 (0.61-0.71)		0.67 (0.62-0.72)	
	40-49	78	121	0.84 (0.70-1.01)		0.83 (0.69-1.00)	
	> 50	191	318	0.88 (0.78-1.00)		0.87 (0.77-0.98)	
High dose Aspirin	1-2	383	780	1	1.14 (1.09-1.19) p < 0.001	1	1.13 (1.08-1.18) p < 0.001
	0	13971	18224	0.61 (0.56-0.65)		0.70 (0.65-0.76)	
	3-9	104	237	1.19 (1.03-1.38)		1.18 (1.02-1.36)	
	10-19	26	59	1.20 (0.92-1.57)		1.18 (0.90-1.54)	
	20-29	9	26	1.42 (0.96-2.10)		1.40 (0.94-2.06)	
	30-39	3	8	1.19 (0.66-2.16)		1.17 (0.65-2.12)	
	40-49	5	11	1.47 (0.73-2.95)		1.44 (0.72-2.89)	
	> 50	7	34	2.60 (1.84-3.66)		2.44 (1.73-3.44)	
Statin	1-2	935	1581	1	0.93 (0.92-0.94) p < 0.001	1	0.93 (0.92-0.95) p < 0.001
	0	12139	15967	0.55 (0.52-0.58)		0.65 (0.61-0.68)	
	3-9	1695	2100	0.75 (0.71-0.81)		0.76 (0.71-0.81)	
	10-19	1606	1582	0.62 (0.58-0.67)		0.63 (0.59-0.68)	
	20-29	1046	979	0.62 (0.57-0.67)		0.63 (0.58-0.68)	
	30-39	805	692	0.59 (0.54-0.65)		0.61 (0.55-0.66)	
	40-49	213	229	0.68 (0.59-0.78)		0.68 (0.60-0.79)	
	> 50	239	355	0.85 (0.75-0.95)		0.84 (0.75-0.95)	
Allopurinol	1-2	245	322	1		1	

	0	13836	18169	0.77 (0.69-0.86)		0.90 (0.80-1.01)	
	3-9	212	226	0.86 (0.73-1.02)	0.96 (0.92-1.00)	0.86 (0.72-1.02)	0.97 (0.93-1.01)
	10-19	153	160	0.86 (0.71-1.04)	p = 0.07	0.87 (0.72-1.05)	p = 0.13
	20-29	15	19	0.74 (0.58-0.93)		0.76 (0.60-0.96)	
	30-39	100	89	0.74 (0.58-0.94)		0.77 (0.61-0.99)	
	40-49	94	83	0.95 (0.60-1.51)		0.96 (0.61-1.53)	
	> 50	24	37	1.07 (0.76-1.51)		1.06 (0.75-1.49)	
Angiotensin agents	1-2	837	1383	1		1	
	0	11851	15513	0.60 (0.57-0.64)		0.69 (0.65-0.73)	
	3-9	1569	2085	0.84 (0.78-0.89)	0.96 (0.94-0.97)	0.84 (0.78-0.90)	0.96 (0.95-0.97)
	10-19	1651	1793	0.71 (0.66-0.76)	p < 0.001	0.72 (0.67-0.77)	p < 0.001
	20-29	1281	1241	0.65 (0.60-0.70)		0.66 (0.61-0.71)	
	30-39	1281	1262	0.68 (0.63-0.73)		0.71 (0.66-0.77)	
	40-49	578	648	0.75 (0.68-0.82)		0.78 (0.71-0.85)	
	> 50	636	812	0.80 (0.74-0.88)		0.82 (0.75-0.90)	

*Trend tests among treated patients.

Table 3. Number of individuals with at least one prescription of the drug (N), risk time, events with a diagnosis of depression or use of antidepressants, hazard ratios (HR) of depression or use of antidepressants adjusted for age, sex, employment status, and calendar year (unadjusted and adjusted for somatic diagnoses).

Variable	Prescription number	Risk time (per 1000 person years)	Events with depression	Unadjusted for somatic diagnoses	Trend test	Adjusted for somatic diagnoses	Trend test
				Hazard ratio (95% CI)	p*	Hazard ratio (95% CI)	p*
Non-aspirin NSAIDs	1-2	12806	211070	1	1.20 (1.20-1.20) p < 0.001	1	1.19 (1.19-1.20) p < 0.001
	0	6955	77089	0.69 (0.68-0.69)		0.71 (0.70-0.72)	
	3-9	7597	206754	1.58 (1.57-1.59)		1.56 (1.55-1.57)	
	10-19	1529	56011	2.03 (2.01-2.05)		1.99 (1.97-2.01)	
	20-29	461	17612	2.04 (2.01-2.07)		1.98 (1.95-2.02)	
	30-39	223	8391	1.95 (1.91-2.00)		1.90 (1.86-1.94)	
	40-49	121	4668	1.97 (1.91-2.03)		1.91 (1.86-1.97)	
	> 50	180	7231	2.03 (1.99-2.08)		1.96 (1.91-2.01)	
Low dose Aspirin	1-2	805	32357	1	0.64 (0.63-0.65)	1	0.93 (0.93-0.94)
	0	10337	162942	0.42 (0.42-0.43)		0.48 (0.47-0.48)	
	3-9	883	28568	0.75 (0.74-0.77)		0.75 (0.74-0.76)	
	10-19	895	25096	0.64 (0.63-0.65)		0.93 (0.93-0.93)	

	20-29	652	18502	0.64 (0.63-0.65)	p < 0.001	0.64 (0.63-0.66)	p < 0.001
	30-39	586	18036	0.69 (0.68-0.70)		0.70 (0.68-0.71)	
	40-49	43	1842	0.83 (0.79-0.87)		0.82 (0.78-0.86)	
	> 50	81	3786	0.84 (0.81-0.87)		0.83 (0.80-0.86)	
High dose Aspirin	1-2	229	7771				
	0	11344	196312	0.58 (0.57-0.60)		0.66 (0.64-0.67)	
	3-9	53	1871	0.97 (0.92-1.02)		0.96 (0.91-1.01)	
	10-19	11	494	1.10 (1.00-1.20)	1.10 (1.00-1.20) p = 0.00435	1.03 (1.01-1.05)	1.03 (1.01-1.05) p = 0.00686
	20-29	4	162	1.08 (0.93-1.27)		1.09 (0.93-1.27)	
	30-39	1	42	1.18 (0.95-1.46)		1.19 (0.96-, 1.47)	
	40-49	2	83	1.04 (0.76-1.41)		1.06 (0.78-1.44)	
	> 50	2	110	1.31 (1.09-1.59)		1.28 (1.06-1.54)	
Statin	1-2	656	26764	1		1	
	0	10073	163347	0.40 (0.39-0.40)		0.46 (0.45-0.46)	
	3-9	1192	31761	0.65 (0.64-0.66)	0.92 (0.92-0.92) p < 0.001	0.65 (0.64-0.66)	0.92 (0.92-0.93) p < 0.001
	10-19	1120	25004	0.55 (0.54-0.56)		0.55 (0.54-0.56)	
	20-29	720	15968	0.56 (0.55-0.57)		0.56 (0.55-0.57)	
	30-39	551	12948	0.59 (0.58-0.60)		0.60 (0.59-0.61)	
	40-49	136	3756	0.64 (0.61-0.66)		0.64 (0.62-0.67)	
	> 50	128	4589	0.72 (0.69-0.74)		0.72 (0.70-0.74)	
Allopurinol	1-2	173	5224	1		1	

	0	11234	193718	0.62 (0.60-0.63)	0.98 (0.97-0.99) p < 0.001	0.71 (0.69-0.73)	0.98 (0.98-0.99) p = 0.002
	3-9	153	4184	0.91 (0.87-0.94)		0.90 (0.87-0.94)	
	10-19	111	2821	0.83 (0.80-0.87)		0.84 (0.80-0.88)	
	20-29	73	1952	0.87 (0.83-0.92)		0.89 (0.85-0.94)	
	30-39	70	1875	0.85 (0.80-0.89)		0.89 (0.84-0.94)	
	40-49	10	362	1.02 (0.92-1.14)		1.04 (0.94-1.16)	
	> 50	14	552	0.99 (0.91-1.08)		1.00 (0.91-1.09)	
Angiotensin agents	1-2	590	22252	1	0.95 (0.95-0.96) p < 0.001	1	0.96 (0.96-0.96) p < 0.001
	0	9821	157397	0.46 (0.45-0.47)		0.52 (0.51-0.52)	
	3-9	1135	30746	0.73 (0.72-0.74)		0.73 (0.72-0.74)	
	10-19	1196	27356	0.62 (0.60-0.63)		0.62 (0.61-0.63)	
	20-29	920	20733	0.60 (0.59-0.62)		0.62 (0.60-0.63)	
	30-39	925	21229	0.62 (0.61-0.63)		0.64 (0.63-0.66)	
	40-49	399	10329	0.67 (0.66-0.69)		0.69 (0.68-0.71)	
	> 50	402	12486	0.74 (0.72-0.76)		0.76 (0.74-0.77)	

*Trend tests among treated patients.

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