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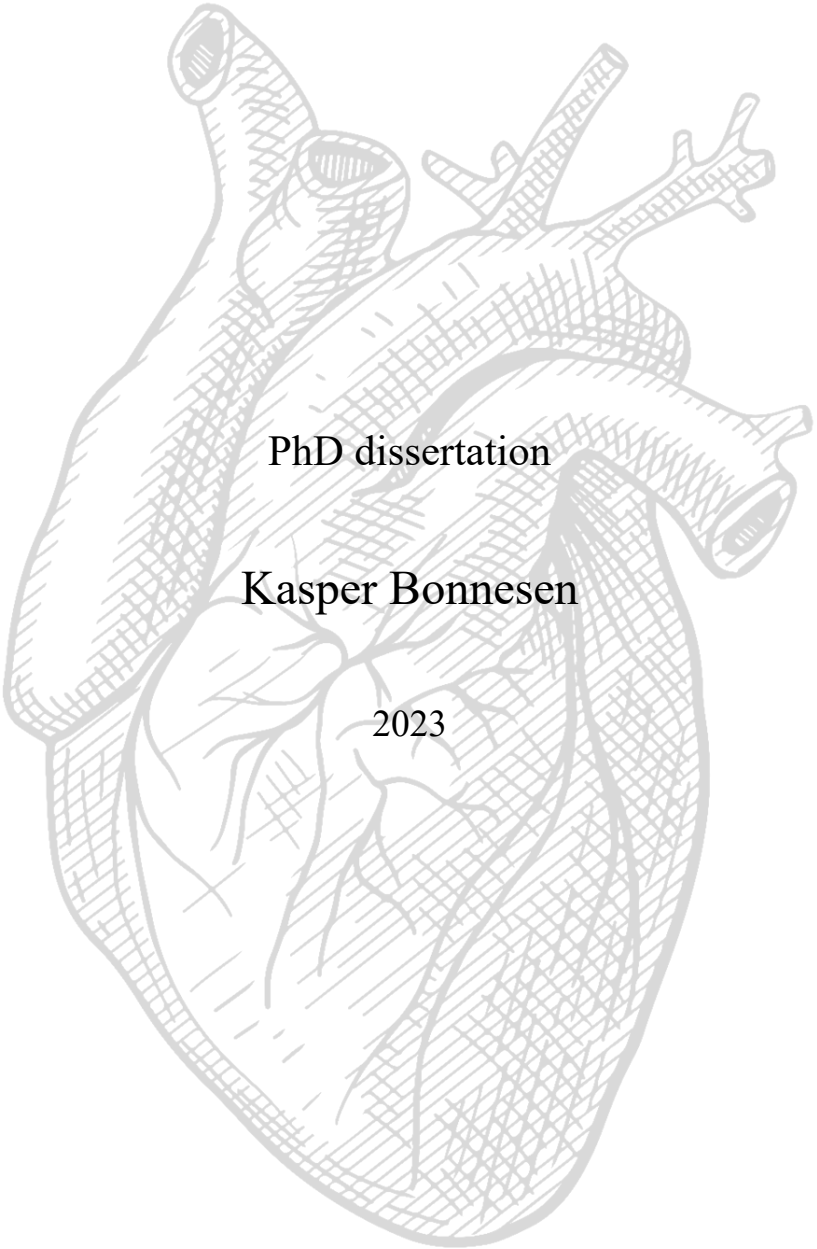
Cardiovascular risks associated with use of non-steroidal anti-inflammatory drugs in individuals with modifiable and socioeconomic cardiovascular risk factors



PhD dissertation

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Als ich can (Jan van Eyck ≈1390–1441)

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Kasper Bonnesen, February 2023

Studies

This dissertation is based on the following three original papers, which will be referred to throughout the dissertation by their Roman numerals (I, II, and III). The studies are presented in full in the Appendices 1 to 3.

Study I: **Bonnesen K**, Ehrenstein V, Grønkjaer MS, Pedersen L, Lash TL, and Schmidt M. Impact of lifestyle and socioeconomic position on use of non-steroidal anti-inflammatory drugs: A population-based cohort study. *Pharmacoepidemiol Drug Saf.* 2022 20221116.

Study II: **Bonnesen K**, Pedersen L, Ehrenstein V, Grønkjaer MS, Sørensen HT, Hallas J, Lash TL, and Schmidt S. Impact of lifestyle and socioeconomic position on the association between non-steroidal anti-inflammatory drug use and major adverse cardiovascular events: a case-crossover study. *Provisionally accepted.* 2022.

Study III. **Bonnesen K**, Pedersen L, Ehrenstein V, Sørensen HT, Lash TL, and Schmidt S. Impact of hemoglobin A1c level on the association between non-steroidal anti-inflammatory drug use and major adverse cardiovascular events in patients with type 2 diabetes: A population-based cohort study. *In review.* 2022.

Abbreviations

BMI	Body mass index
CI	Confidence interval
COX	Cyclooxygenase
HbA1c	Hemoglobin A1c
HR	Hazard ratio
IPTW	Inverse probability of treatment weight
LABKA	The Clinical Laboratory Information System
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
rDANCAMI	The Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases
RLRR	The Register of Laboratory Results for Research
RR	Relative risk

Content

1. Introduction

1.1 Non-steroidal anti-inflammatory drugs

1.1.1 Mechanisms of action

Non-steroidal anti-inflammatory drugs (hereafter, *NSAIDs*) prevent the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane by inhibiting two isoforms of the cyclooxygenase (COX) enzyme: isoform 1 (COX-1) and 2 (COX-2).[1] This reduction in prostaglandin production provides relief from pain and inflammation, but it also leads to a higher risk of gastric ulcers[2] due to increased hydrochloric acid production and decreased blood flow to the gastric mucosa.[3, 4]

1.1.2 NSAIDs and cardiovascular risks

The development of COX-2 selective NSAIDs, also known as coxibs, was thought to resolve the issue of increased risk of gastric ulcers with NSAIDs.[1] Unlike COX-1, COX-2 is not responsible for gastric mucosa protection and is upregulated in inflammatory conditions rather than being continuously expressed, making it a more desirable analgesic, antipyretic, and anti-inflammatory target.[1] However, later research revealed that many NSAIDs, selective COX-2 inhibitors as well as non-selective NSAIDs,[5] increased the risk of several cardiovascular events,[6-11] including myocardial infarction,[8, 9, 12] ischemic stroke,[8, 9] congestive heart failure,[10] and atrial fibrillation.[11] The mechanisms behind this increased risk are thought to involve a complex altered equilibrium between COX-1 and COX-2 expression,[1] which increases thrombogenesis,[1] elevates blood pressure,[1, 13] and changes cardiac rhythmicity.[1] Although no clear association between COX-2 selectivity and cardiovascular risk seems to exist,[8, 9] low doses of non-selective NSAIDs, such as ibuprofen ≤1200 mg per day and naproxen ≤500 mg per day, are considered safer than more COX-2 selective NSAIDs, such as diclofenac and coxibs.[7] A large meta-analysis of observational studies found that low-dose ibuprofen (relative risk [RR]=0.99, 95% confidence interval [CI]: 0.89–1.10) and low-dose naproxen (RR=0.97, 95% CI: 0.87–1.09) did not increase cardiovascular risk.[7] In contrast, high-dose ibuprofen (RR=1.29, 95% CI: 0.99–1.66), high-dose naproxen (RR=1.14, 95% CI: 0.95–1.38), low (RR=1.26, 95% CI: 1.08–1.46) and high-dose diclofenac (RR=1.59, 95% CI: 1.22–2.26), as well as low and high-dose of the coxibs celecoxib, rofecoxib, etoricoxib, and valdecoxib did carry an increased cardiovascular risk.[7]

1.1.3 Recommendations for NSAID use

In 2016, the European Society of Cardiology recommended exercising caution when using NSAIDs for patients with existing or at high risk for cardiovascular disease.[14] They also recommended to use low-dose ibuprofen or low-dose naproxen over more COX-2 selective NSAIDs.[14] The basis for these recommendations is the assumption of greater absolute risk increases with NSAID use due to higher underlying risks rather than empirical evidence.

1.1.4 Trends in NSAID use

In Denmark, NSAID sales have remained steady for two decades with total NSAID sales around 30 defined daily doses per 1000 individual per day and around 14% of the population filling at least one NSAID prescription each year.[15] Meanwhile, total NSAID sales have increased in the other Nordic countries, with sales rising by 48% in Sweden, 30% in Norway, 24% in Finland, and 7% in Iceland.[15] As a result, total NSAID

sales per 1000 individuals per day are around 55 defined daily doses in Sweden, 45 in Norway, and 75 in Finland and Iceland.[15] Frequent NSAID use is also seen in many other countries worldwide.[16-18]

Thus, the recommendation to exercise caution when using NSAIDs has not noticeable impacted total sales, however, the recommendation to avoid COX-2 selective NSAIDs may have changed sales patterns.[15] Today, the only NSAID available over-the-counter in Denmark is 200 mg ibuprofen tablets sold in packs of 20.[19] Despite always being the most used NSAID in the Nordic countries,[15] ibuprofen's share has increased in recent years**,** from 53% in 2005 to 77% in 2015 in Denmark.[15] Likewise, in 2005, diclofenac accounted for 21% of total sales in Denmark, but only for 9% in 2015.[15] Celecoxib and rofecoxib were the only coxibs prescribed in Denmark between 2000 and 2005, both accounting for approximately 1% of all filled NSAID prescriptions,[19] but are no longer prescribed since 2005.[19] This trend is not seen in other Nordic countries such as Iceland[15] or in North America,[18] Asia,[18] or Oceania,[18] where more COX-2 selective NSAIDs still are frequently sold.

Despite these changes in prescription patterns, NSAIDs are still commonly prescribed to people with manifest cardiovascular disease.[20] In Denmark, 14% of individuals receiving a first-time cardiovascular disease diagnosis, fills an NSAID prescription within a year.[20] This proportion is around 10% for those with myocardial infarction, ischemic stroke, congestive heart failure, and atrial fibrillation.[20]

1.2 Modifiable and socioeconomic risk factors

1.2.1 Definition

In individuals without established cardiovascular disease, healthcare providers aim to prevent its development by considering and addressing each person's cardiovascular risk profile.[21] This profile is, besides age and sex, based on modifiable factors such as cholesterol levels, blood pressure, smoking, type 2 diabetes, obesity, alcohol consumption, and physical inactivity.[21] Additionally, socioeconomic factors like marital status,[22, 23] low income,[24, 25] short education,[23-29] and unemployment,[29-31] can also impact cardiovascular disease and worsen its prognosis.[21]

1.2.2 Contribution of the development of cardiovascular disease

The presence of modifiable risk factors greatly contributes to an increased risk of cardiovascular disease. For instance, smoking has been linked to a 190% increased risk of myocardial infarction,[32] type 2 diabetes with hemoglobin A1c (HbAc1) levels ≥53 mmol/mol with a 140% increased risk of coronary heart disease,[33] every 5 kg/m^2 increase in body mass index (BMI) with a 40% increased risk of vascular mortality,[34] drinking ≥60 grams of alcohol per day with a 70% increased risk of ischemic stroke,[35] and physical inactivity with a 70% increased risk of cardiovascular mortality in men and a 140% increased risk in women.[36] The fact that modifiable risk factors often coexist[37] is of great concern as it leads to an even higher risk of cardiovascular disease.[38] Data from the Framingham Heart Study (Table 1)[38] shows that accumulation of risk factors substantially increases the risk of cardiovascular disease in both males and females of all ages. For example, a 50-year-old male with no modifiable risk factors has a 5% chance of developing coronary heart disease within the next 10 years, but if he has a Framingham Heart Score of 10, his risk jumps to 25%.

The management of one risk factor is often influenced by the presence of others. For example, in patients with type 2 diabetes, treating hypertension and dyslipidemia is of utmost importance.[39] Additionally, some risk factors can increase the risk of others. For instance, there is a clear correlation between an increase in BMI and the risk of type 2 diabetes.[39] It is important to note that type 2 diabetes is a heterogeneous disease,[40] which means that its cardiovascular risk may vary between individual phenotypes.

Socioeconomic factors also play a role in increasing the risk of cardiovascular disease. Being unmarried has been linked with a 40% increased risk of death due to coronary heart disease,[22] short education with a 30% increased risk of myocardial infarction,[25] low income with an over 200% increased risk of sudden cardiac death,[24] and unemployment with a 40% increased risk of fatal and non-fatal coronary heart disease.[29] A lower socioeconomic position likely increases cardiovascular risk both directly and indirectly through lower adaptation of a healthy lifestyle[41, 42] and reduced use of healthcare services.[42] Thus, clinicians should consider each patient's cardiovascular risk profile before treating pain or inflammation with NSAIDs.

Table 1. Relative and absolute 10-year risks of coronary heart disease in males and females in their fifties according to Framingham scoring (modified from "Prediction of coronary heart disease using risk factor categories" by Wilson et al.)[43]

	Relative risks				Absolute risks	
	Male		Female		Male	Female
Low-risk level*	**5%**	**7%**	**5%**	**7%**		
Framingham scoring†	**Age 50–54**	**Age 55–59**	**Age 50–54**	**Age 55–59**		
0	‡	‡	‡	‡	2%	2%
1	‡	‡	‡	‡	3%	2%
2	‡	‡	‡	‡	4%	3%
3	1.0	‡	‡	‡	5%	3%
4	1.4	1.0	‡	‡	7%	4%
5	1.6	1.1	‡	‡	8%	4%
6	2.0	1.4	1.0	‡	10%	5%
7	2.6	1.9	1.2	‡	13%	6%
8	3.2	2.3	1.4	1.0	16%	7%
9	4.0	2.9	1.6	1.1	20%	8%
10	5.0	3.6	2.0	1.4	25%	10%
11	6.1	4.4	2.2	1.6	31%	11%
12	7.4	5.2	2.6	1.9	37%	13%
13	9.0	6.4	3.0	2.1	45%	15%
≥14	>10.6	>7.6	3.6	2.6	>53%	18%

*Ten-year absolute risk of coronary heart disease for an individual of the same age with blood pressure <120/<80 mmHG, total cholesterol 160–199 mg/dL, HDL cholesterol ≥55 mg/dL, no smoking, and no type 2 diabetes

†Points given for age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and type 2 diabetes

‡No individuals with such profile due to Framingham scoring points for age

1.2.3 Importance in overall burden of disease

The impact of modifiable and socioeconomic risk factors on global health is substantial.[44] The Global Burden of Disease Study estimates that there are between 8 and 9 million deaths each year attributed to smoking, around 5 million to high BMI, between 2 and 3 million to high alcohol use, and around 1 million to physical inactivity.[44] Additionally, over 535 million people have type 2 diabetes, a number projected to increase to 640 million by 2030 and 780 million by 2045.[45]

Type 2 diabetes alone is responsible for around 7 million deaths each year.[45] Despite this, less than 20% of patients might be within the target HbA1c level of <53 mmol/mol,[46] even after starting second-line therapy.[47] The large number of patients with type 2 diabetes, many of whom are dysregulated, raises concern as it increases the risk of both micro- and macro-vascular complications,[39] with higher HbA1c levels being linked to heightened risk of coronary heart disease[33] and mortality.[48] For example, compared with individuals without type 2 diabetes, patients with HbAc1 ≥53 mmol/mol might have a 140% increased risk of coronary heart disease, while those with HbAc1 <53 mmol/mol might only have a 61% increased risk.[33] Similarly, patients with type 2 diabetes and HbAc1 ≥75 mmol/mol might have a 38% higher risk of all-cause mortality

compared with patients with HbA1c <53 mmol/mol, while patients with HbA1c 53–75 mmol/mol might not have an increased risk.[48]

1.3 Gap in knowledge

There is limited knowledge on the effect of NSAIDs on cardiovascular disease in individuals with modifiable and socioeconomic risk factors, creating three significant gaps in understanding. The first gap is the limited understanding of NSAID use by individuals with risk factors but without manifest disease.[49] This makes it uncertain if the observed cardiovascular risks associated with NSAID use in observational studies can be partially attributed to the presence of these risk factors. The second gap is the absence of studies investigating the cardiovascular risks of NSAIDs in individuals with modifiable and socioeconomic risk factors but without manifest disease, leaving it undetermined if caution should be exercised in those without established cardiovascular disease. The third gap is the limited knowledge of the risks associated with NSAIDs in patients with type 2 diabetes.[50, 51] The few studies previously examining the cardiovascular risks from NSAIDs in patients with type 2 diabetes did not consider whether this varied according to HbA1c levels, leading to uncertainty about whether all patients with type 2 diabetes should exercise caution when using NSAIDs, or only a specific subgroup.

2. Literature review

I conducted literature searches on MEDLINE using the advanced search builder on PubMed. The search results were limited to studies written in English and published after the year 2000. The relevance of the studies was determined on the title, abstract, and full text, in that order. I also reviewed the references and co-citations (through CoCite),[52] and included additional relevant literature not previously identified. The results of the literature reviews are summarized in Tables 2 to 4 and the search algorithms used are presented in the table footnotes. I elaborate further on these results below.

2.1 Study I: Risk factors and NSAID use

Health registries often lack information on modifiable and socioeconomic risk factors, which hinder the ability to control for these factors in observational studies when exploring the association between NSAID use and cardiovascular events. This limitation has been recognized in several observational studies examining such associations.[53-66] It thus remains uncertain whether confounding by modifiable and socioeconomic risk factors could contribute to the increased cardiovascular risk seen in observational studies of NSAID use, and thereby to the discrepancy between these studies[7, 12] and randomized clinical trials,[67] determining the cardiovascular risks of NSAIDs.

It is currently unknown if there is an association between modifiable and socioeconomic risk factors and NSAID use, as only one study has explored this topic and found that individuals with a socioeconomic disadvantage were prescribed fewer NSAIDs compared with those with a socioeconomic advantage.[49] Other studies have looked at the association between modifiable and socioeconomic risk factors and general drug use, but the results have been inconsistent.[67-86] For instance, the risk of polypharmacy (concomitant use of ≥5 prescription drugs) has been found to be increased by 340% in individuals with a BMI ≥30 kg/m,[274] by 105% in those with low income,[72] and by 10% to 55% in those with low level of education.[74, 83, 84] Similarly, unemployment has been linked to a higher use of prescription and over-the-counter drugs compared with those who are employed.[85] Meanwhile, frequent alcohol consumption has been associated with a 35% decreased risk of polypharmacy[72] and marital status has been shown not associated with the risk of polypharmacy.[74, 84] The relationship between smoking and the risk of polypharmacy is unclear, with one study linking it to a 60% increased risk,[74] while another found no association.[72]

If the frequency of NSAID use varies between individuals with and without modifiable and socioeconomic risk factors, it could indicate that these risk factors may play a role in the elevated cardiovascular risk observed in observational studies of NSAID use.[7, 12] Hence, understanding the relationship between modifiable and socioeconomic risk factors and NSAID use is crucial as it could provide context to previous observational studies and guide the design of future studies investigating the cardiovascular risks associated with NSAID use.

Table 2. Study I literature review

Author, journal, year	Design, setting, period	Study population (size, disease, age)	Exposure, outcome, effect measure	Main findings (effect estimate, 95% confidence interval)
Downing et al.[67] BMJ open 2022	Cross-sectional U.K. 2015–2016, 2018	n=5509	E: Smoking, alcohol consumption, education, income, employment O: Polypharmacy (5–9 used drugs) EM: Odds ratio	Increased risk of polypharmacy for ex-smoking (1.29, 1.00–1.66), regular alcohol consumption (0.66, 0.51–0.85), having dept (0.66, 0.49–0.88), and working (0.69, 0.51–0.94)
Schmidt and Pottegård[87] Eur Heart J Cardiovasc Pharmacother 2021	Cohort Denmark 1996–2017	n=628,834 d: CVD	E: Comorbidities O: Filling ≥1 NSAID prescription <1 year after first-time CVD EM: Odds ratio	The proportion filling an NSAID prescription was 14% overall, 9% for MI, 10% for IS, 9% for HF, 11% for AF, and 17% for VTE Increased risk of filling an NSAID prescription for obesity (1.32, 1.27–1.37), diabetes (1.06, 1.03–1.09), hypertension (1.03, 1.00–1.05), COPD (1.24, 1.22–1.26), sleep apnea (1.37, 1.29–1.46), osteoporosis (0.90, 0.87–0.94), rheumatoid arthritis (1.48, 1.40–1.56), systemic connective tissue disease (1.08, 1.03–1.13), and osteoarthritis (1.53, 1.49–1.56)
Van Oort et al.[68] Diabet Med 2021	Cross-sectional The Netherlands 2009–2015	n=6759 d: Type 2 diabetes	E: BMI, smoking, alcohol consumption, education O: Moderate polypharmacy (5–9 used drugs), severe polypharmacy (≥10 used drugs) EM: Odds ratio	Primary care: Increased risk of polypharmacy for each 5 kg/m^2 increase in BMI (1.55, 1.40–1.72), light-to-moderate (0.50, 0.39–0.64) and heavy alcohol consumption (0.60, 0.41–0.89), and middle (0.62, 0.47–0.83) and high level of education (0.47, 0.34–0.66) Academic care: Increased risk of severe polypharmacy for each 5 kg/m^2 increase in BMI (1.52, 1.38–1.67), former smoking (2.10, 1.63–2.70), light-to-moderate alcohol consumption (0.47, 0.37–0.59), and middle (0.58, 0.44–0.77) and high level of education (0.38, 0.29–0.51)
Davies et al.[49] PLoS One 2021	Cross-sectional U.K. 2006	n=845 y: ≥85	E: Socioeconomic advantage (Index of Multiple Deprivation) O: Polypharmacy (n used prescription drugs) EM: Odds ratio	Socioeconomic disadvantage: Lower risk of NSAID polypharmacy (0.37, 0.17–0.84) Socioeconomic advantage: Lower risk of polypharmacy for calcium channel blockers (0.41, 0.19–0.92) and ACE-inhibitors (0.52, 0.28–0.96); higher risk of polypharmacy for tricyclic and related antidepressants (2.98, 1.15–7.75) and beta-2 agonists (2.33, 1.02–5.36)
Silva et al.[69] Rev Bras Epidemiol 2020	Cross-sectional Brazil 2008–2010	n=14,523 y: 35–74	E: Education, income O: Polypharmacy (≥5 used drugs) EM: Odds ratio	Lower risk of polypharmacy for household income quartile 1 (0.51, 0.41–0.65), 2 (0.52, 0.42–0.64), 3 (0.67, 0.55–0.82), and 4 (0.84, 0.70–0.99)
Bakhriansyah et al.[88] J Clin Pharm Ther 2019	Case-control The Netherlands 1986–2005	n MI: 970 n controls: 2974 d: MI y: ≥18	E: NSAIDs O: MI EM: Odds ratio	A logistic regression model conditioning on age, sex, comorbidity burden, and drug use and another logistic regression model further conditioning on BMI, smoking status, exercise level, and alcohol use generated comparable results for the association between NSAID use and MI for selective COX-2 inhibitors (1.07, 0.52–2.18 vs. 1.08, 0.52–2.22) and conventional NSAIDs (0.93, 0.77–1.12 vs. 0.89, 0.73–1.09)
Kennel et al.[70] BMC Cardiovasc Disord 2019	Cross-sectional U.S. 2003–2014	n=947 d: HF y: ≥50	E: Smoking, education, income, marital status, living situation O: Hyper-polypharmacy (≥10 used drugs) EM: Prevalence ratio	Higher risk of hyper-polypharmacy for high school or below (1.74, 1.01–2.99) and income <$20,000 (1.70, 1.01–1.21)

Rawle et al.[71] BMC Geriatr 2018	Cross-sectional U.K. 2014–2015	n=2001 y: 69	E: Education, social class O: Polypharmacy (5–8 prescribed drugs), extreme polypharmacy (≥9 prescribed drugs) EM: Relative risk ratio	Lower risk of polypharmacy (0.3, 0.2–0.5) and extreme polypharmacy (0.2, 0.1–0.5) for A-level or higher education
Slater et al.[72] BMJ open 2018	Cross-sectional U.K. 2012–2013	n=7730 y: ≥50	E: BMI, smoking, alcohol consumption, income O: Polypharmacy (5–9 prescribed drugs), hyper-polypharmacy (≥10 prescribed drugs) EM: Odds ratio	Associations with polypharmacy for BMI ≥30 (1.81, 1.53–2.15); rare (0.76, 0.61–0.94), frequent (0.65, 0.53–0.79), and very frequent alcohol consumption (0.64, 0.52–0.78); and wealth quantile 4 (1.23, 1.02–1.5) and 5 (1.28, 1.04–1.69) Associations with hyper-polypharmacy for BMI ≥30 (2.28, 1.63–3.21); rare (0.70, 0.50–0.99), frequent (0.40, 0.29–0.56), and very frequent alcohol consumption (0.39, 0.27–0.55); and wealth quantile 4 (1.75, 1.17–2.60), and 5 (2.04, 1.34–3.11)
Sarwar et al.[73] Medicina (Kaunas) 2018	Cross-sectional Pakistan 2017–2018	n=385 y: ≥65	E: Education O: Polypharmacy (5–9 used drugs) EM: Odds ratio	Higher risk of polypharmacy for no formal (1.20, 1.03–2.15) and primary education (1.18, 1.01–1.54)
Castioni et al.[74] BMC Health Serv Res 2017	Cross-sectional Switzerland 2009–2012	n=4938	E: BMI, smoking, education, marital status O: Polypharmacy (≥5 used drugs) EM: Odds ratio	Increased risk of polypharmacy for BMI 25–29 (2.09, 1.65–2.66) and BMI ≥30 (4.38, 3.39–5.66), former (1.42, 1.14–1.75) and current smoking (1.63, 1.25–2.12), and low level of education (1.56, 1.17–2.07)
Randhawa et al.[75] PLoS One 2017	Cross-sectional U.S. 1988–2012	n=57,543	E: BMI O: Use of antibiotics, analgesics, lipid-lowering drugs, antidepressants, antidiabetics, antihypertensives EM: Odds ratio	Increased risk of use of antihypertensives and antidiabetics for BMI 25–29 and ≥30 (odds ratios presented in a forest plot)
Husson et al.[76] J Nutr Health Aging 2014	Cross-sectional France 2004–2009	n=2545 y: ≥60	E: BMI, alcohol consumption, physical activity, education O: Polypharmacy (≥4 used drugs) EM: Odds ratio	Increased risk of polypharmacy for metabolic syndrome (3.17, 1.95–5.15), lack of physical activity (1.50, 1.00–2.26), and low or medium level of education (2.20, 1.24–4.30)
Gao et al.[37] PLoS One 2013	Cross-sectional China 2009–2010	n=46,683	E: Alcohol consumption, physical activity, NSAID use, diet O: Clustering of 4 CVD risk factors (≥2 of: hypertension, diabetes, dyslipidemia, overweight) EM: Odds ratio	Increased risk of CVD risk factor clustering for NSAID use (2.17, 1.84–2.55)
Sigurdardottir et al.[77] Scandinavian journal of public health	Cross-sectional Iceland Period not reported	n=186 y: ≥65	E: Education, income, living situation O: Polypharmacy (n used drugs categorized as alimentary tract and metabolism,	No associations were observed

2013			blood and blood-forming organs, cardiovascular system, and nervous system drugs) EM: Odds ratio	
Santos et al.[78] Rev Saude Publica 2013	Cross-sectional Brazil 2009–2010	n=934 y: ≥60	E: Education, income, marital status O: Polypharmacy (n used drugs) EM: Prevalence ratio	Increased risk of polypharmacy for being widowed (1.5, 1.2–1.9)
Neves et al.[79] Rev Saude Publica 2013	Cross-sectional Brazil 2009	n=400 y: ≥60	E: BMI, physical activity, education, income, marital status, living situation O: Polypharmacy (≥5 used drugs) EM: Odds ratio	Increased risk of polypharmacy for 1–4 (5.28, 2.14–13.0) and 5–9 y schooling (2.43, 1.00–5.86)
Papa et al.[80] Eur J Clin Pharmacol 2011	Cross-sectional Greece 2006	n=968 y: >18	E: BMI, smoking, alcohol consumption, education, employment, marital status O: Drug utilization (≥1 used drug), polypharmacy (≥4 used drugs) EM: Odds ratio	Increased risk of drug utilization for university education (2.3, 1.1–4.8) Increased risk of polypharmacy for BMI ≥30 (3.8, 1.2–12) and smoking (3.0, 1.2–8.1)
Kutsal et al.[81] J Am Med Dir Assoc 2009	Cross-sectional Turkey 2007–2008	n=1430 y: ≥65	E: Education, marital status, retirement status O: Polypharmacy (n used drugs) EM: None	Associations with polypharmacy for marriage (p=0.009) and retirement (p<0.001)
Moen et al.[82] Ann Pharmacother 2009	Cross-sectional Sweden 2001–2005	n=2816 y: 30–49, 50–64, 65–75	E: BMI, smoking, alcohol consumption, physical activity, education, marital status O: Multiple drug use (25% of the study group with the highest n used prescription drugs) EM: Odds ratio	Overall: Increased risk of multiple drug use for BMI ≥30 (2.3, 1.3–3.9) y 40–64: Increased risk of multiple drug use for current smoking (1.9, 1.0–3.5)
Haider et al.[83] J Am Geriatr Soc 2009	Cross-sectional Sweden 2005	n=626,258 y: 75–89	E: Education O: Polypharmacy (≥5 used drugs), excessive polypharmacy (≥10 used drugs) EM: Odds ratio	Increased risk of polypharmacy for medium (1.06, 1.04–1.07) and low level of education (1.11, 1.10–1.12) Increased risk of excessive polypharmacy for medium (1.08, 1.05–1.10) and low level of education (1.15, 1.13–1.17)
Haider et al.[84] Clin Ther 2008	Cross-sectional Sweden 2002	n=621 y: ≥77	E: Education, income, occupation, marital status, living situation O: Polypharmacy (use of ≥5 prescription drugs) EM: Odds ratio	Increased risk of polypharmacy for ≤8 y education (1.39, 0.95-2.04) and living in institution (3.44, 2.23–4.55)
Schneeweiss et al.[89] Epidemiology 2005	Cohort U.S. 1995	n=8785 y: ≥65	E: Selective COX-2 inhibitors (celecoxib or rofecoxib) before and after adjusting for BMI, smoking, education, income, and aspirin use O: MI	Left uncontrolled, BMI, smoking, education, income, and aspirin use bias the risk of MI towards the null when comparing selective COX-2 inhibitors with non-selective NSAIDs (-1.56%), non-use (-0.54%), naproxen (-1.86%), or rofecoxib (-3.15%)

			EM: Odds ratio	
Nielsen et al.[85] Eur J Clin Pharmacol 2003	Cross-sectional Denmark 2000	n=16,690 y: ≥16	E: Education, income, employment O: Over-the-counter and prescription drug use EM: Odds ratio	Overall: Increased risk of use of prescriptions drugs for being a disability pensioner (2.2, 1.8–2.7) or low income (1.2, 1.1–1.4); increased risk of use of over-the-counter drugs for medium income (1.1, 1.0–1.2) In men: Increased risk of use of prescriptions drugs for 11–12 (0.8, 0.7–0.9) or 13–14 y schooling (0.8, 0.7–1.0)
Perry and Turner[86] J Woman Aging 2001	Cross-sectional U.S. 1988–1994	n=5249 y: ≥65	E: Education, income O: Polypharmacy (n used prescription drugs) EM: None	Level of education accounted for 7.4% and income accounted for 0.4% of the variance in polypharmacy

Abbreviations: ACE, acetylcholine esterase; AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CVD, cardiovascular disease; E, exposure; EM, effect measure; HF, heart failure; IS, ischemic stroke; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; n, number; O, outcome; VTE, venous thromboembolism; y, years of age

Search algorithms: (((lifestyle[MeSH Terms]) OR (factor, socioeconomic[MeSH Terms])) OR (socioeconomic status[MeSH Terms])) AND (polypharmacy[MeSH Terms]), (((lifestyle[MeSH Terms]) OR (factor, socioeconomic[MeSH Terms])) OR (socioeconomic status[MeSH Terms])) AND (agents, non steroidal anti inflammatory[MeSH Terms])

2.2 Study II: Impact of risk factors on NSAID-associated cardiovascular risks

There is a lack of knowledge on how modifiable and socioeconomic risk factors impact the cardiovascular risks of NSAIDs as previous studies primarily have focused on the associations between NSAIDs and cardiovascular events in patients with existing cardiovascular diseases, such as coronary heart disease,[55, 56, 63, 90-96] congestive heart failure,[97-99] atherothrombosis,[100, 101] or atrial fibrillation.[102] Because people have different baseline *absolute* risks based on the presence or absence of risk factors, it is possible that the *relative* increase associated with NSAID use could also differ between individuals with and without these risk factors.

Regular users of NSAIDs often have modifiable and socioeconomic risk factors,[37] as well as diseases such as rheumatoid arthritis, osteoarthritis, osteoporosis, and back pain, which might prompt their use of NSAIDs.[87, 103, 104] The reason that these diseases and risk factors tend to occur together might be because modifiable and socioeconomic risk factors increase the likelihood of developing these diseases.[105-110]

Given the large impact of modifiable and socioeconomic risk factors on public health, it is essential to understand the potential variations in cardiovascular risks of NSAIDs among individuals with and without these risk factors. Such knowledge may guide prescription patterns in countries where NSAIDs are primarily obtained via prescription, like Denmark, and inform general drug use recommendations in countries where they are more readily available over-the-counter, like the United States.

Table 3. Study II literature review

Author, journal, year	Design, setting, period	Study population (size, disease, age)	Exposure, outcome, effect measure	Main findings (effect estimate, 95% confidence interval)
Wang et al.[111] Cancer Res 2018	Meta-analysis (case-control, cohort) Multinational (Europe, North America) Period not reported	n colorectal: 11,894 n controls: 15,999	E: NSAIDs O: Colorectal cancer EM: Odds ratio	Decreased risk of colorectal cancer for NSAID use (0.77, 0.71–0.83), which was not modified by BMI, smoking status, alcohol consumption, physical activity level, or dietary habits
Schjerning Olsen et al.[90] Jama 2015	Cohort Denmark 2002–2011	n=61,971 30-day MI survivors y: ≥30	E: NSAIDs O: CVD (CVD death, non-fatal re-MI, non-fatal stroke) EM: Hazard ratio	Increased rate of CVD for ibuprofen when used alone (1.42, 1.28–1.57) and in combination with aspirin (1.50, 1.33–1.70), clopidogrel (2.38, 1.54–3.67), and both aspirin and clopidogrel (1.20, 1.00–1.57) Increased rate of CVD for diclofenac when used alone (1.65, 1.44–1.90) and when used in combination with aspirin (1.75, 1.44–2.08) and both aspirin and clopidogrel (1.74, 1.24–2.45)
Schjerning Olsen et al.[63] Eur Heart J Cardiovasc Pharmacother 2015	Cohort Denmark 1997–2011	n=128,751 MI y: ≥30	E. NSAIDs O: AF EM: Hazard ratio	Increased rate of AF for low (1.33, 1.13–1.57) and high-dose ibuprofen (1.26, 0.90–1.76), high-dose naproxen (1.51, 0.90–2.37), and low (1.23, 0.97–1.56) and high-dose diclofenac (1.55, 0.92–2.62)
Lamberts et al.[102] Ann Intern Med 2014	Cohort Denmark 1997–2011	n=150,900 AF y: ≥30	E: NSAIDs O: Thromboembolism EM: Hazard ratio	Increased rate of thromboembolism for NSAIDs in patients without antiplatelet treatment (1.22, 1.08–1.37), with single antiplatelet treatment (1.25, 1.13–1.37), with oral anticoagulant treatment (1.67, 1.41–1.98), and with combined single antiplatelet and oral anticoagulant treatment (1.41, 1.07–1.85)
Kohli et al.[101] Am J Med 2014	Cohort Multinational (Europe) 2003–2004	n=44,095 Stable AT disease or ≥3 AT risk factors y: ≥45	E: NSAIDs O: CVD EM: Hazard ratio	NSAIDs were associated with increased rate of non-fatal MI (1.37, 1.12–1.68), non-fatal stroke (1.21, 1.00–1.45), and HF (1.18, 1.03–1.34)
Barthélémy et al.[100] Int J Cardiol 2013	Cohort Multinational (Europe) 2003–2004	n=23,728 Stable AT disease or ≥3 AT risk factors y: ≥45 years of age	E: NSAIDs O: cMACCE (CVD death, non-fatal MI, non-fatal stroke) EM: Odds ratio	Increased risk of cMACCE for NSAIDs (1.15, 0.94–1.41)
Schjerning Olsen et al.[92] PLoS One 2013	Cohort Denmark 1997–2009	n=97,698 MI y: ≥30	E: NSAIDs O: CVD EM: Odds ratio	Ibuprofen was associated with increased risk of cardiovascular death (≈1.3), a composite of non-fatal MI and coronary death (≈1.3), and a composite of non-fatal and fatal stroke (≈1.2) Naproxen was associated with increased risk of a composite of non-fatal MI and coronary death (≈1.4)
Schjerning Olsen et al.[55] Circulation 2012	Cohort Denmark 1997–2009	n=99,187 MI y: ≥30	E: NSAIDs O: CVD (coronary death, non-fatal re-MI) EM: Hazard ratio	Ibuprofen was associated with increased rate of CVD <1 (1.23, 1.11–1.36), <2, <3, <4, and <5 years Naproxen was associated with increased rate of CVD <1 (1.44, 1.07–1.94) and <2 years Diclofenac was associated with increased rate of CVD <1 (1.57, 1.36–1.83), <2, <3, <4, and <5 years

Schjerning Olsen et al.[56] Circulation 2011	Cohort Denmark 1997–2006	n=83,677 MI y: ≥30	E: NSAIDs O: CVD (all-cause death, non-fatal re-MI) EM: Hazard ratio	Ibuprofen was associated with increased rate of CVD after 7–14 (1.57, 1.27–1.94), 14–30, 30–90, and >90 days Naproxen was associated with increased rate of CVD after >90 days (1.55, 1.10–2.17) Diclofenac was associated with increased rate of CVD after 0–7 (3.52, 2.93–4.20), 7–14, 14–30, 30–90, and >90 days
Bavry et al.[93] Am J Med 2011	Cohort Multinational (countries not reported) 1997–2003	n=22,576 Hypertension, coronary artery disease	E: NSAIDs O: CVD (all-cause death, non-fatal MI, non-fatal stroke) EM: Hazard ratio	Chronic NSAID use was associated with increased rate of all-cause mortality (1.89, 1.53–2.35), CVD mortality (2.26, 1.70–3.01), and MI (1.66, 1.21–2.28)
Schmidt et al.[94] Pharmacotherapy 2011	Cohort Denmark 2002–2005	n=13,001 Stent implantation	E: NSAIDs O: MACE (MI, stent thrombosis, target-lesion revascularization, cardiac death) EM: Hazard ratio	No association between non-selective NSAIDs and MACE (1.04, 0.83–1.31)
Ray et al.[91] Circ Cardiovasc Qual Outcomes 2009	Cohort U.K., U.S., Canada 1999–2004	n=48,566 MI, revascularization, unstable angina pectoris	E: NSAIDs O: Serious coronary heart disease (MI, out-of-hospital death from coronary heart disease), serious CVD (all-cause death, non-fatal MI, non-fatal stroke) EM: Incidence rate ratio	Increased rate of serious coronary heart disease for high-dose ibuprofen (1.35, 0.97–1.87) and low-dose diclofenac (1.65, 1.13–2.42) Increased rate of serious CVD or death for low (1.13, 0.92–1.37) and high-dose ibuprofen (1.14, 0.95–1.38) and low (1.43, 1.14–1.78) and high-dose diclofenac (1.34, 1.09–1.65)
Gislason et al.[99] Archives of internal medicine 2009	Cohort + case-crossover Denmark 1995–2004	n=107,092 HF	E: NSAIDs O: MI, HF, all-cause death EM: Hazard ratio	Increased rate of MI for low (1.31, 1.15–1.48) and high-dose ibuprofen (1.47, 1.15–1.89), low (1.47, 1.02–2.10) and high-dose naproxen (1.62, 0.97–2.72), and low (1.14, 0.91–1.43) and high-dose diclofenac (2.43, 1.74–3.40) Increased rate of HF for low (1.16, 1.09–1.23) and high-dose ibuprofen (1.18, 1.04–1.33), low (1.18, 0.97–1.44) and high-dose naproxen (1.18, 0.88–1.57), and low (1.34, 1.21–1.48) and high-dose diclofenac (1.42, 1.17–1.73) Increased rate of all-cause death for high-dose ibuprofen (2.83, 2.64–3.02), high-dose naproxen (1.97, 1.64–2.36), and low (1.31, 1.20–1.42) and high-dose diclofenac (5.54, 5.08–6.03) The results from the case-crossover analysis were consistent
Gislason et al.[95] Circulation 2006	Cohort + case-crossover Denmark 1995–2002	n=58,432 MI	E: NSAIDs O: Re-MI, all-cause death EM: Hazard ratio	Increased rate of re-MI for low (1.28, 1.03–1.60) and high-dose ibuprofen (1.22, 0.99–1.51) and low (1.27, 0.92–1.76) and high-dose diclofenac (1.89, 1.40–2.55) Increased rate of all-cause death for high-dose ibuprofen (2.20, 1.95–2.48) and high-dose diclofenac (4.44, 3.79–5.19) The results from the case-crossover analysis were consistent
Feenstra et al.[97] Archives of internal medicine 2002	Cohort The Netherlands 1990–1993	n=345 HF y: ≥55	E: NSAIDs O: Re-HF EM: Relative risk	No association between re-HF and NSAIDs (1.4, 0.5–3.8)

Abbreviations: AF, atrial fibrillation; AT, atherothrombotic; BMI, body mass index; E, exposure; EM; effect measure; cMACCE, major adverse cardiovascular and cerebrovascular event; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; n, number; NSAID, non-steroidal anti-inflammatory drug; O, outcome; y, years of age

Search algorithms: (((lifestyle[MeSH Terms]) OR (factor, socioeconomic[MeSH Terms])) OR (socioeconomic status[MeSH Terms])) AND (agents, non steroidal anti inflammatory[MeSH Terms]), ((effect modification[MeSH Terms]) OR (interaction[MeSH Terms])) AND (agents, non steroidal anti inflammatory[MeSH Terms]), (agents, non steroidal abortifacient[MeSH Terms]) AND (cardiovascular disease[MeSH Terms])

2.3 Study III: Impact of glycemic regulation on NSAID-associated cardiovascular risks

It is estimated that 40% of patients with type 2 diabetes suffer from back pain,[103] 15% have osteoarthritis,[103] and up to 5% have rheumatoid arthritis,[104] leading to common use of NSAIDs. In Denmark, type 2 diabetes has been associated with a 6% increased risk of filling an NSAID prescription within a year after first-time cardiovascular disease.[20]

Despite their frequent use, there is a lack of knowledge regarding the potential differences in cardiovascular risks associated with NSAID use among patients with type 2 diabetes. Although studies have shown higher risk of cardiovascular disease[50] and increase in HbA1c[51] associated with NSAID use in patients with type 2 diabetes, no study has specifically looked at the differences in risk based on glycemic regulation. As patients with type 2 diabetes have different baseline *absolute* risks due to factors such as HbA1c, it is possible that the *relative* risk increase associated with NSAID use may also vary among these patients.

Therefore, given the substantial number of patients with type 2 diabetes who have uncontrolled blood glucose levels, it is very important to gain insights into the effect of glycemic regulation on the cardiovascular risks associated with NSAID use as it would clarify whether the current recommendation to avoid NSAIDs in patients with type 2 diabetes[14] is relevant for all or only a subgroup of patients.

Table 4. Study III literature review

Author, journal, year	Design, setting, period	Study population	Exposure, outcome, effect measure	Main findings (effect estimate, 95% confidence interval)
Pearson-Stuttard et al.[103] eClinicalMedicine 2022	Cross-sectional (series) U.K. 2000–2019	n≈224,000 Type 2 diabetes	Not applicable	In 2019: Back pain prevalence ≈40% and osteoarthritis prevalence ≈16%
Tsujimoto and Kajio[112] Diabetes Obes Metab 2019	Cohort Japan Period not presented	n=3600 Type 2 diabetes + history of MI, angina pectoris, coronary or other revascularization, stroke	E: NSAIDs (stratified by aspirin use) O: All-cause death EM: Hazard ratio	Decreased rate of all-cause death for aspirin among NSAID non-users (0.80, 0.69–0.93), but not among NSAID users (1.35, 0.85–2.13)
Nowakowska et al.[104] BMC Med 2019	Cohort U.K. 2007–2017	n=102,394 Type 2 diabetes	Not applicable	Rheumatoid arthritis prevalence: 2.1% in most deprived and 2.4% in least deprived men and 4.3% in most deprived and 4.7% in least deprived women Osteoporosis prevalence: 0.7% in most deprived and 0.6% in least deprived men and 3.7% in most deprived and 3.3% in least deprived women
Kim et al.[50] BMJ Open Diabetes Res Care 2015	Cohort Republic of Korea 2008–2012	n=117,610 Type 2 diabetes y: ≥65	E: NSAIDs O: CVD (MI, IS) EM: Incidence rate ratio	Increased rate of CVD for NSAIDs (1.21, 1.17–1.26)
Tsai et al.[113] Diabet Med 2015	Cohort Taiwan 2007–2011	n=48,715 Type 2 diabetes + CKD y: ≥30	E: NSAIDs O: CKD EM: Hazard ratio	Increased rate of CVD for NSAIDs when taken for 1–89 (1.28, 1.20–1.35) and ≥90 days (1.37, 1.26–1.49), when taking ≥1 DDD/day (1.29, 1.21–1.38), and when taking 1–15 (1.25, 1.16–1.33) and ≥16 DDDs in 1 year (1.33, 1.25–1.42)
Wami et al.[51] Br J Gen Pract 2013	Cohort Belgium 1994–2008	n=3416 Type 2 diabetes y: ≥30	E: NSAIDs O: HbA1c level EM: Odds ratio	Increased risk of an increase in HbA1c for NSAIDs among patients treated with diet only (1.34, 1.14–1.58), oral drugs (1.36, 1.13–1.62), and both diet and oral drugs (1.34, 1.05–1.70)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DDD, defined daily dose; E, exposure; EM, effect measure; HbA1c, hemoglobin A1c; IS, ischemic stroke; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; n, number; O, outcome; y, years of age

Search algorithms: (type 2 diabetes mellitus[MeSH Terms]) AND (agents, non steroidal anti inflammatory[MeSH Terms]), (hemoglobin a 1[MeSH Terms]) AND (agents, non steroidal anti inflammatory[MeSH Terms])

3. Hypotheses and aims

Study I: Risk factors and NSAID use
Our hypothesis was that individuals with modifiable and socioeconomic risk factors would use NSAIDs more often compared with those without such risk factors. Our aim was to study the association between modifiable and socioeconomic risk factors and the initiation and use of NSAIDs.

Study II: Impact of risk factors on NSAID-associated cardiovascular risks
We hypothesized that the relative increase in cardiovascular risk associated with NSAID use would be lower in individuals with modifiable and socioeconomic risk factors compared with those without such risk factors. The aim of our study was to investigate the impact of modifiable and socioeconomic risk factors on the association between NSAID use and cardiovascular events in individuals without manifest cardiovascular disease.

Study III: Impact of glycemic regulation on NSAID-associated cardiovascular risks
Our hypothesis was that in patients with type 2 diabetes, the relative increase in cardiovascular risk associated with NSAID use would be lower in those with dysregulated blood glucose compared with those with well-regulated blood glucose. Our aim was to examine the association between NSAID use and cardiovascular events among subgroups of patients with type 2 diabetes based on their HbA1c level.

Table 5. Overview of study methods

Section	Study I	Study II	Study III
Data sources	CRS, DNHS, ISR, IDLMR, DNPR, NPR	CRS, DNHS, ISR, IDLMR, DNPR, NPR	CRS, DNPR, NPR, LABKA, RLRR, DRCD
Design	Nationwide, population-based cohort study	Nationwide, population-based case-crossover study	Nationwide, population-based cohort study
Period	May 2010–December 2019	May 2010–December 2019	January 2012–December 2020
Population	First-time 2010, 2013, or 2017 DNHS responders (≥18 y)	First-time DNHS (2010, 2013, 2017) responders (≥18 y) experiencing outcome	First-time HbA1c ≥48 mmol/mol (≥18 y)
Exclusion criteria	NSAID use (≤3 months)	NSAID use (≤12 months), CVD history	Diabetes history, NSAID use (≤12 months), CVD history
Exposure	BMI, smoking, alcohol consumption, binge drinking, physical activity, marital status, education, income, employment	Ibuprofen, naproxen, diclofenac (half DDD, 30-day gap)	Ibuprofen, naproxen, diclofenac (half DDD, 14-day gap)
Outcomes	NSAID initiation (time-to first filled prescription), NSAID use (number of filled prescriptions <1 year)	Myocardial infarction, ischemic stroke, congestive heart failure, all-cause death	Myocardial infarction, ischemic stroke, congestive heart failure, atrial fibrillation or flutter, all-cause death, CVD death
Effect modifiers	None	BMI, smoking, alcohol consumption, binge drinking, physical activity, marital status, education, income, employment (baseline)	HbA1c (updated)
Co-variables	Sex, age, comorbidities, drug use, modifiable and socioeconomic cardiovascular risk factors (baseline)	None	Sex, age, comorbidities, drug use (baseline)
Controlling strategies	Regression	Self-controlled	Inverse probability of treatment weighting
Statistical analyses	Fine and Gray's estimator, Cox proportional-hazards regression, cumulative odds model, multiple imputation, inverse probability of participation weighting	Mantel-Haenszel	Pooled logistic regression
Subgroup analyses	(1) Intermittent or chronic NSAID use, (2) healthcare-seeking behavior, (3) contraindications to NSAID use, (4) sex, (5) age	None	(1) Sex, (2) age, (3) non-cardiovascular comorbidity burden
Sensitivity analyses	(1) Changing outcome to ibuprofen, naproxen, and diclofenac, (2) using the last instead of the first survey when >1 surveys were completed, (3) changing index date from 1 May to 1 January and 1 September in survey year, (4) excluding individuals with NSAID use ≤12 months before survey, (5) adjusting for diabetes with chronic complications also using prescription information to define the disease	(1) Changing gap to 14 days, (2) changing gap to 60 days, (3) changing exposure to daily tablets no matter the dose (3 for ibuprofen, 2 for naproxen, 2 for diclofenac)	(1) Changing gap to 30 days, (2) changing exposure too full DDD, (3) changing exposure to daily tablets no matter the dose (3 for ibuprofen, 2 for naproxen, 2 for diclofenac), (4) stratifying on baseline HbA1c without update

Abbreviations: BMI, body mass index; CRS, Central Registration System; CVD, cardiovascular disease; DDD, defined daily dose; DNHS, Danish National Health Survey; DNPR, Danish National Patient Registry; DRCD, Danish Register of Causes of Death; HbA1c, hemoglobin A1c; IDLMR, Integrated Database for Labor Market Research; ISR, Income Statistics Register; LABKA, Clinical Laboratory Information System; NPR, Danish National Prescription Registry; NSAID, non-steroidal anti-inflammatory drugs; RLRR, Register of Laboratory Results for Research; y, years of age

4. Methods

Table 5 presents an overview of the study methods. I elaborate on each element below.

4.1 Setting

The Danish healthcare system provides universal tax-financed health services to all Danish citizens and legal residents.[114] These services include free access to general practitioners and hospitals as well as partial reimbursement for the costs of prescribed drugs.[114] All Danish citizens and legal residents receive at birth or upon emigration a unique Civil Personal Register number, which functions as a personal identifier across all Danish healthcare registries.[115] This number thereby allows linkage of Danish healthcare registries on an individual level.[115]

4.2 Data sources

The data sources used in each study are summarized below and in Table 6.

The Danish Civil Registration System was established in 1968 and is daily updated with information on mortality and migration, thereby providing virtually complete long-term follow-up with accurate censoring at death or upon emigration of all Danish citizens and legal residents.[115]

The Danish National Health Survey is a nationwide survey containing ≥52 questions administered in 2010, 2013, 2017, and 2021 to one national and five regional stratified random samples of approximately 300,000 individuals ≥16 years of age.[116] We had information from the 2010, 2013, and 2017 surveys. The response rate was 60% in 2010, 54% in 2013, and 59% in 2017.[116] The surveys were administered between the end of January and the beginning of May in the survey years, but the surveys do not contain information on the exact date of the response.[116] The surveys include questions on height and weight, smoking status, alcohol consumption, physical activity level, marital status, level of education, income, and employment status.[116] Supplementary Table 1 presents the categorization of the modifiable and socioeconomic risk factors used in the studies.

The Income Statistics Register was established in 1970 and is yearly updated with nationwide information on salaries, fortunes, taxes, public transfers, and pensions.[117]

The Integrated Database for Labor Market Research was established in 1981 and is yearly updated with nationwide information on employment status.[118]

The Danish National Patient Registry contains nationwide information on discharge diagnoses on all non-psychiatric inpatient contacts since 1977 and information on all psychiatric inpatient, psychiatric and non-psychiatric outpatient clinic, and emergency department contacts since 1995.[119] Each contact is registered with one primary diagnosis supplemented by secondary diagnoses if relevant.[119] The diagnoses are coded according to the International Classification of Diseases 8th edition until 1993 and according to the 10th edition since 1994.[119] Each contact is further coded with information on time (*e.g.*, date of hospital admission, hospital discharge, and outpatient clinic contact) and until 2018 type of contact (inpatient, outpatient clinic, or emergency department).[119] Since 2019, the type of contact was not available in the registry. We therefore

used an algorithm based on hospital length to differentiate between inpatient and outpatient clinic contacts.[120] Supplementary Table 2 presents all diagnosis codes used in the studies.

The Danish National Prescription Registry contains nationwide information on all filled prescriptions from community pharmacies since 1995.[121] Each filled prescription contains information on the date of filling, the type of drug (coded according to the Anatomical Therapeutical Chemical code), the number of tablets per package, the number of packages, and the numerical strength per tablet.[121] The registry does not contain information on the indication for treatment or the daily use or length of treatment.[121] Supplementary Table 2 presents all drug codes used in the studies.

The Clinical Laboratory Information System (LABKA)[122] and the *Register of Laboratory Results for Research* (RLRR)[123] contain results from blood samples analyzed in general practices and hospitals in the Central and North Denmark Region since 1997 (LABKA) and nationwide since 2015 (RLRR). Each analysis contains information on the date, the type (coded according to the Nomenclature, Properties, and Units coding system), the value, and the unit (*e.g.*, mmol/mol, mg/L, or %) of the test.[122, 123] The Nomenclature, Properties, and Units system requires that laboratory results are coded with information including the part of the human body undergoing examination (*e.g.*, urine, plasma, or secret), the component measured in the sample (*e.g.*, calcium, ethanol, or glucose), relevant kind-of-property (*e.g.*, substance concentration, mass fraction, or arbitrary content), and unit of measurement.[124]

The Danish Register of Causes of Death contains computerized information on the main underlying cause and potential contributory cause(s) of deaths since 1970 [125]

Table 6. Overview of data sources used in each study

Register	Variables	Study
Danish Civil Registration System	Sex, age	1, 2, 3
Danish National Health Surveys	BMI, smoking, alcohol consumption, binge drinking, physical activity, marital status, education, healthcare seeking behavior*, indication for intermittent NSAID use†	1,2
Income Statistics Register	Income	1, 2
Integrated Database for Labor Market Research	Employment	1, 2
Danish National Patient Registry	Quan-modified Charlson Comorbidity Index comorbidities‡,[126] rDANCAMI comorbidities§,[127] additional comorbidities‖, outcomes¶, indication for chronic NSAID use**, contraindication to NSAID use††	1, 2, 3
Danish National Prescription Registry	NSAID use, drug use‡‡	1, 2, 3
Clinical Laboratory Information System	HbA1c	3
Danish Register of Causes of Death	Cause of death	3

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; NSAID, non-steroidal anti-inflammatory drug; rDANCAMI, the Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases

*Recent visit to a general practitioner

†Bothered by limb pain, shoulder pain, neck pain, back pain, headache, and/or migraine

‡Congestive heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, diabetes with chronic complications, hemi or paraplegia, renal disease, any malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, and AIDS/HIV

§High-risk cancer, low-risk cancer, coagulopathy, obesity, dementia, alcohol and drug abuse, schizophrenia, affective disorder, epilepsy, neurodegenerative disorder, hemiplegia, chronic pulmonary disease, ulcer disease, mild liver disease, moderate to severe liver disease, chronic pancreatitis, and connective tissue disease

‖Hypertension, rheumatic disease, osteoarthritis, rheumatoid arthritis, and isolated hemiplegia,

¶Myocardial infarction, ischemic stroke, congestive heart failure, and atrial fibrillation or flutter

**Osteoarthritis and rheumatoid arthritis

††Congestive heart failure and peptic ulcer disease

‡‡Antiplatelets, anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium channel blockers, diuretics, statins, glucocorticoids, opioids, paracetamol, antimigraine, and proton pump inhibitors

4.3 Designs and populations

Figures 1, 3, and 5 display flowcharts of the study cohorts and Figures 2, 4, and 6 depict the study designs, including the assessment of the exposures, the outcomes, and the co-variables.

4.3.1 Study I: Risk factors and NSAID use

Study I was a nationwide, population-based cohort study, including all adult (≥18 years of age) first-time responders to the Danish National Health Surveys of 2010, 2013, or 2017.[116] We excluded individuals who were already using NSAIDs at the time of their survey response because prevalent and new NSAID users may have different cardiovascular risks. As the exact date of survey response was not available,[116] May 1 in the survey response year was chosen as the index date. This date was chosen because the surveys were conducted between January and May in the corresponding years. Consequently, individuals who passed away before May 1 in the survey year were not included in the study.

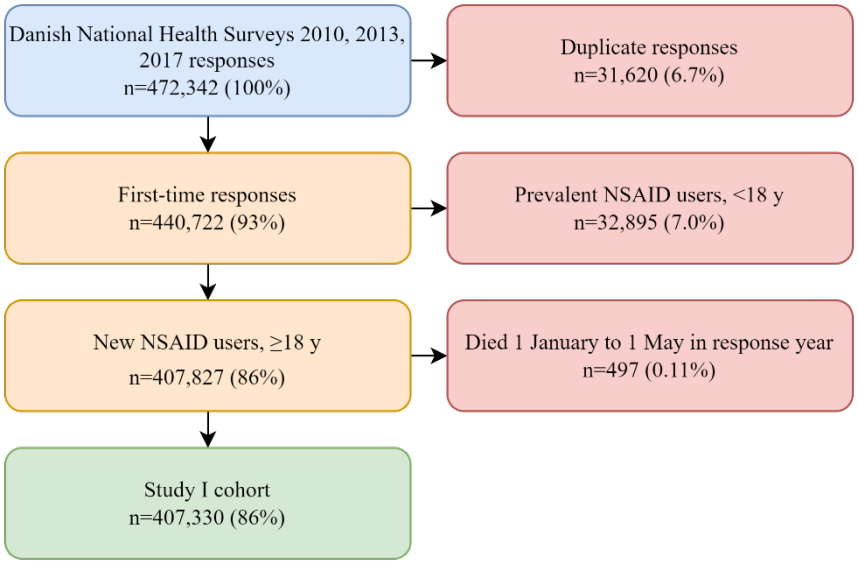
4.3.2 Study II: Impact of risk factors on NSAID-associated cardiovascular risks

Study II was a nationwide, population-based case-crossover study, including all adult (≥18 years of age) first-time responders to the Danish National Health Surveys of 2010, 2013, or 2017,[116] who experienced an outcome. Like in Study I, individuals who were already using NSAID**s** and individuals who passed away before May 1 in the survey year were not included in the study. Additionally, individuals with a prior diagnosis of any cardiovascular disease were also not included in the study.

4.3.3 Study III: Impact of glycemic regulation on NSAID-associated cardiovascular risks

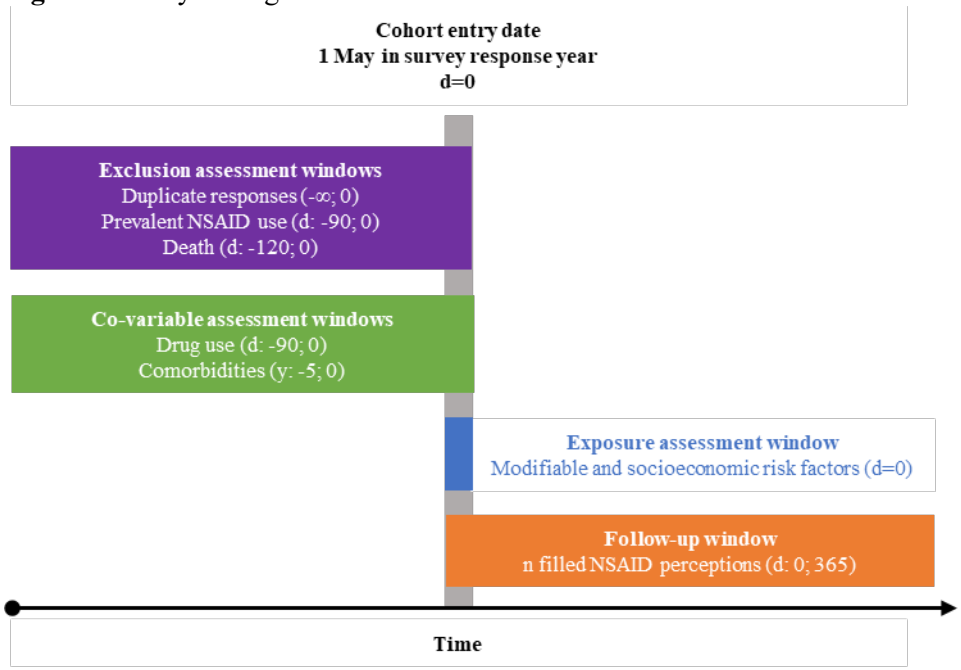
Study III was a nationwide, population-based cohort study, including all adults (≥18 years of age) with a first-time HbA1c measurement ≥48 mmol/mol in the LABKA or the RLRR from January 1, 2012 to December 31, 2020.[122, 123] To ensure that the first HbA1c measurement was not influenced by prior treatment, individuals with a previous diabetes diagnosis or filling of an antidiabetic drug prescription were not included in the study. Furthermore, individuals with a previous diagnosis of myocardial infarction, ischemic stroke, congestive heart failure, or atrial fibrillation or flutter were also not included in the study.

Figure 1. Study I flowchart



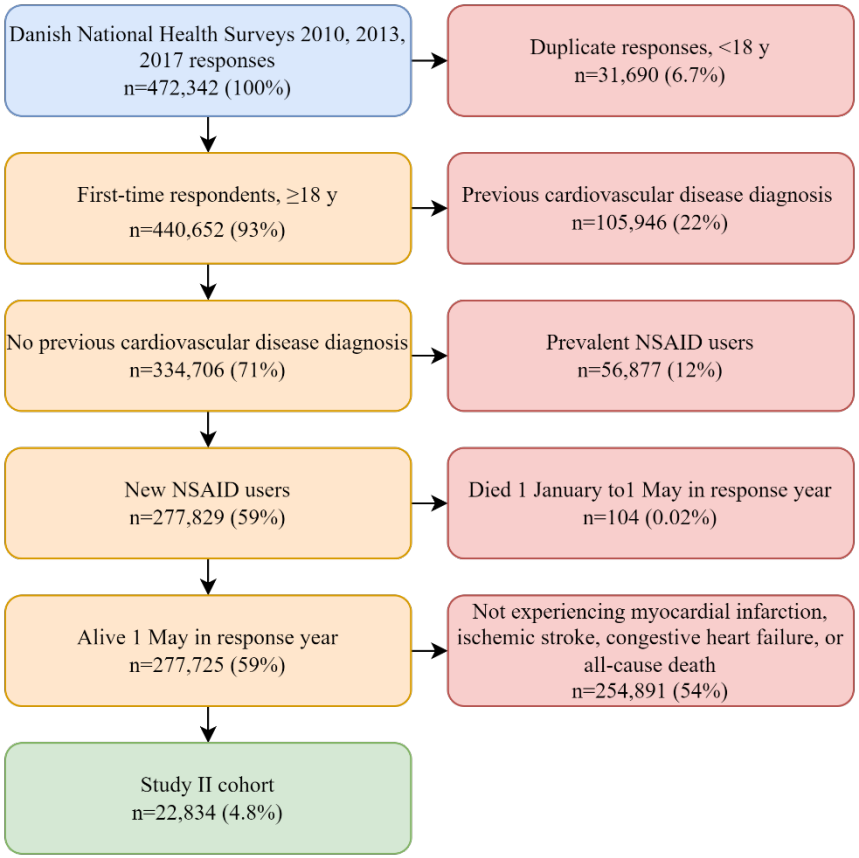
Abbreviations: NSAID, non-steroidal anti-inflammatory drug; n, number; y, years of age

Figure 2. Study I design



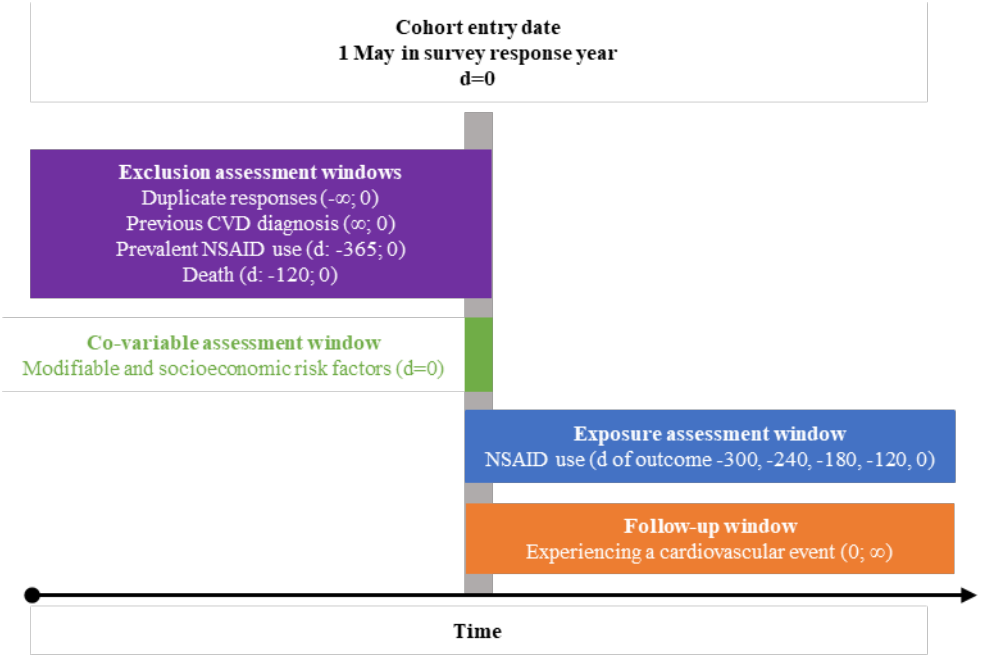
Note: ∞ indicate use of all available data (back to 1977 for diagnoses and 1995 for prescriptions)
Abbreviations: d; day; NSAID, non-steroidal anti-inflammatory drug; y, year

Figure 3. Study II flowchart



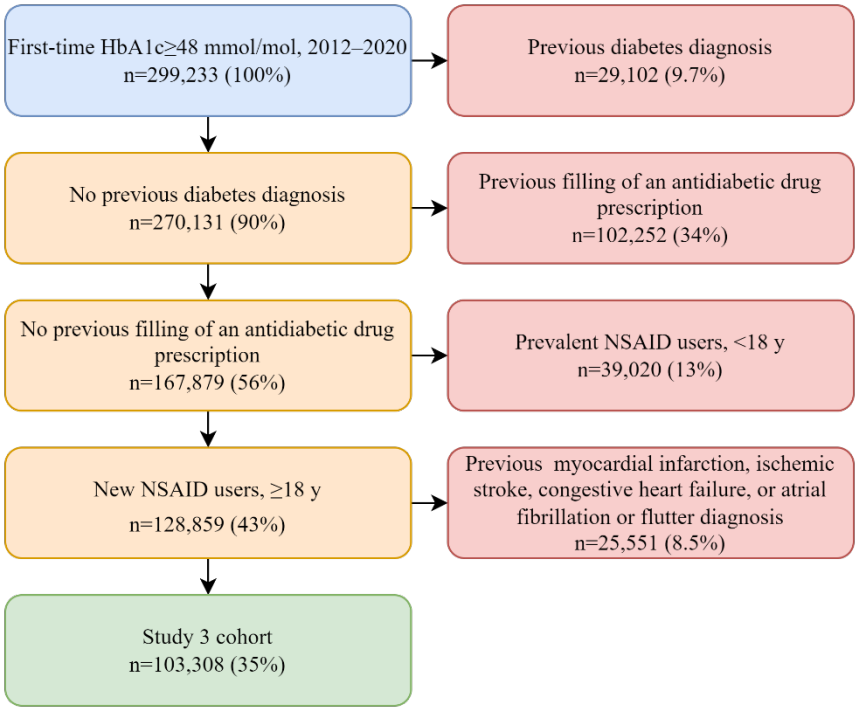
Abbreviations: NSAID, non-steroidal anti-inflammatory drug; n, number; y, years of age

Figure 4. Study II design



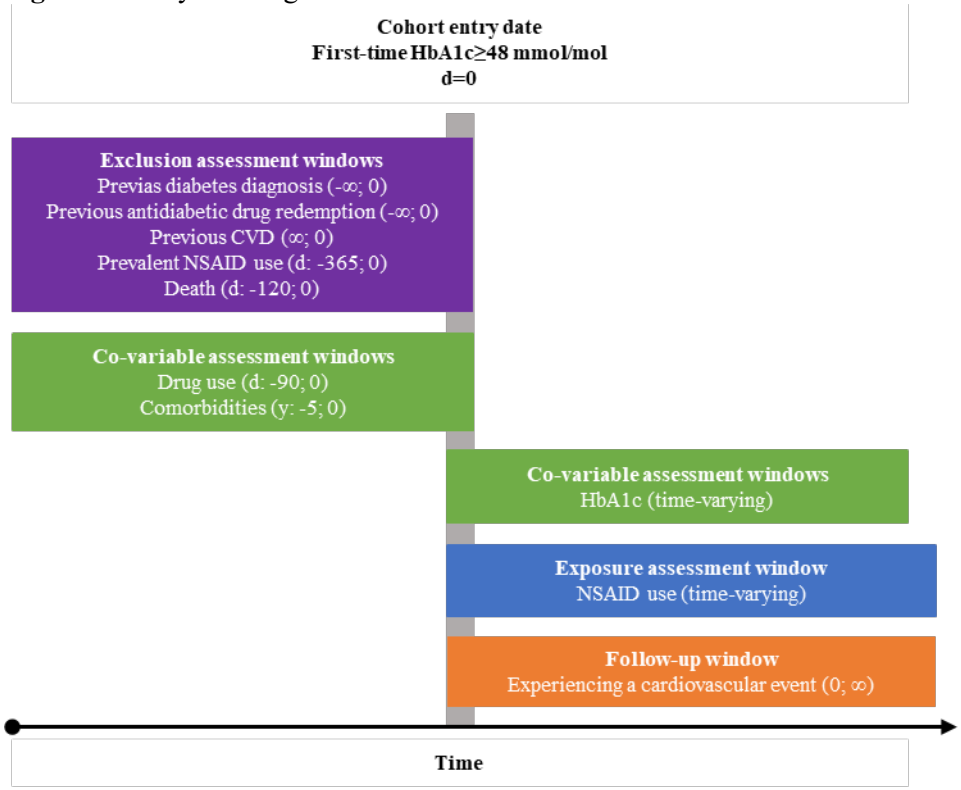
Note: ∞ indicate use of all available data (back to 1977 for diagnoses and 1995 for prescriptions and forward to myocardial infarction, ischemic stroke, congestive heart failure, or all-cause death)
Abbreviation: CVD, cardiovascular disease; d, day; NSAID, non-steroidal anti-inflammatory drug

Figure 5. Study III flowchart



Abbreviations: NSAID, non-steroidal anti-inflammatory drug; n, number; y, years of age

Figure 6. Study III design



Note: ∞ indicate use of all available data (back to 1977 for diagnoses and 1995 for prescriptions and forward to myocardial infarction, ischemic stroke, congestive heart failure, atrial fibrillation or flutter, or all-cause death and HbA1c)

Abbreviation: CVD, cardiovascular disease; d, day; HbA1c, hemoglobin A1c; NSAID, non-steroidal anti-inflammatory drug; y, year

4.4 Exposures

4.4.1 Modifiable and socioeconomic risk factors

In Study I, the exposures of interest were determined by self-reported information on BMI, smoking, alcohol consumption, binge drinking, physical activity, marital status, and education, as well as registry data on income and employment.

4.4.2 NSAID use

In Study II, the exposure of interest was overall use of NSAIDs, while in Study III the exposures were the NSAID subtypes ibuprofen, naproxen, and diclofenac. The use of NSAIDs was determined in a time-varying manner, meaning that an individual was considered an NSAID user from the time they filled a prescription until the end of a use period. The use period was defined as the number of days covered by a prescription, calculated as the filled quantity divided by half of the maximum daily dose when prescribed for pain or fever according to the Danish guidelines (600 mg for ibuprofen, 500 mg for naproxen, and 100 mg for diclofenac). If a patient filled a new prescription within a use period plus a gap period (30 days in Study II and 14 days in Study III), their use period was extended by the number of days provided by the new prescription.

4.5 Outcomes

4.5.1 NSAID initiation and use

In Study I, there were two main outcomes. The first outcome was NSAID initiation, which we defined as the time to first filling of an NSAID prescription. The second outcome was NSAID use, which was defined as the number of filled NSAID prescriptions within a year after survey response.

4.5.2 Cardiovascular events

Studies II and III had a composite cardiovascular event as their main outcome. The composite outcome in Study II consisted of myocardial infarction, ischemic stroke, congestive heart failure, and all-cause death. In Study III, the composite outcome expanded to include atrial fibrillation or flutter in addition to the aforementioned events. In both Studies II and III, the secondary outcomes included the individual cardiovascular events, and Study III also included cardiovascular death as a secondary outcome.

4.6 Co-variables

4.6.1 Confounding

In Studies I and III, the co-variables age, sex, comorbidity burden, and drug use were considered potential confounders. In addition, Study I also considered modifiable and socioeconomic risk factors potential confounders. Due to the self-controlled design, Study II did not consider any co-variables potential confounders. Table 6 presents the included comorbidities, drugs, and modifiable and socioeconomic risk factors.

4.6.2 Effect measure modification

In Study I, we considered reasons for intermittent or chronic NSAID use, healthcare-seeking behavior, contraindications to NSAID use, sex, and age potential effect modifiers. In Study II, we examined potential effect modification by modifiable and socioeconomic risk factors in the main analyses. In Study III, we considered HbA1c level a potential effect modifier in the main analyses and sex, age, and non-cardiovascular comorbidity burden potential effect modifiers in the subgroup analyses.

4.7 Statistical analyses

For the data management, SAS version 9.4 (SAS Institute Inc.) was used in alle studies, while statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) in Study I and Stata version 17 (StataCorp LLC) in all studies. Visualization was done using STATA in all studies and R version 4.2.2 (The R Foundation) in Study III. Categorical variables were presented as numbers with percentages and continuous variables as medians with interquartile ranges. All estimates were presented with a 95% confidence level. The main statistical analyses used in the studies are described below.

4.7.1 Cumulative incidence

In Study I, the cumulative incidence of NSAID initiation was calculated for subgroups defined by modifiable and socioeconomic risk factors using a Fine and Gray estimator.[128] The reason for this was that death was considered a competing risk, and using a Kaplan-Meier estimator[129] in such cases would lead to overestimation of cumulative incidence proportions.[130] This is due to the loss of the one-to-one relationship between the cause-specific and the sub-distributional risk,[130] which increases with the incidence of the competing risk and the time of follow-up.

4.7.2 Cox proportional-hazards regression

In Study I, a Cox proportional-hazards regression[131] was used to compute cause-specific hazard ratios (HRs) of the association between modifiable and socioeconomic risk factors and the time to NSAID initiation after survey response. The choice of whether to model the effect of the exposure of interest on the cause-specific or sub-distributional hazard is unclear in the presence of competing risk.[132] Modelling the effect of the cause-specific hazard (as done with a Cox proportional-hazards regression) would estimate the effect among those currently event free.[132, 133] The proportional-hazards assumption was assessed using log-log plots.

4.7.3 Cumulative odds model

In Study I, the association between modifiable and socioeconomic risk factors and the number of NSAID prescriptions filled within a year after survey response was estimated using a cumulative odds model.[134] The odds ratios (ORs) calculated from this model indicate the likelihood of filling *k* rather than *0 to k-1* prescriptions.[135] An OR above 1 indicated that persons exposed to the risk factors had an increased risk of filling one additional prescription compared with those unexposed.

4.7.4 Missing data

In Study I, the proportion of missing values on the modifiable and socioeconomic risk factors ranged from 0.74% for employment to 13% for binge drinking frequency. To handle missing values, multiple imputation

was used.[136] Missing data can come in three forms: missing completely at random, missing at random, and missing not at random.[137] If the data is missing completely at random, both complete-case and multiple imputation analyses will (disregarding random error) produce estimates close to the true value — assuming no other bias.[137] When data is missing at random (*i.e.*, the pattern of the missing data can be explained by the observed data) a complete-case analyses will produce biased estimates and multiple imputation is required.[137] On the other hand, if the data is missing not at random (*i.e.*, there is no pattern of the missing data or a pattern that cannot be explained by the observed data) both complete-case and multiple imputation analyses will produce biased estimates.[137] Unfortunately, the nature of the missing data cannot be determined, since the data is in fact missing.

4.7.5 Inverse probability of participation weighting

In study I, differences in survey response rates between males and females and age groups were addressed by using inverse probability of participation weighting.[138] This method gives everyone a weight corresponding to the inverse of the probability of them responding to the survey.

4.7.6 Mantel-Haenszel method

In Study II, a self-controlled case-crossover design was used to examine the impact of exposure to NSAID use on the outcome date among those who experienced the outcome.[139] ORs were calculated using a Mantel-Haenszel method,[139] by dividing the number of patients exposed to NSAID use on the outcome date but not on a reference date by the number of patients exposed to NSAID use on a reference date but not on the outcome date. The reference dates used were 120, 180, 240, and 300 days before the outcome date. The case-crossover design was chosen because it eliminates confounding by time-stable factors such as genetics by making each patient their own control.[139] Figure 7 illustrates the case-crossover design.

4.7.7 Pooled logistic regression

In Study III, a pooled logistic regression[140] was used to assess the association between NSAID use and cardiovascular events. When the probability of experiencing the outcome in each period is rare, like in Study III, the ORs generated from the pooled logistic regression can be interpreted as HRs.[140] The pooled logistic regression was chosen to circumvent the built-in selection bias of the Cox proportional-hazards regression.[141]

4.7.8 Inverse probability of treatment weighting

In Study III, the follow-up of all individuals was divided into weekly time periods. For each period, the inverse probability of treatment weight (IPTW) for exposure to each NSAID (ibuprofen, naproxen, or diclofenac) was calculated.[142] A logistic regression model incorporating the period identifier and relevant co-variables was used to calculate the IPTW denominator. A separate logistic regression model, only incorporating the period identifier, was used to calculate the IPTW numerator. This approach generated stabilized IPTWs. The stabilized IPTWs were cumulated across all periods for each participant to create time-varying stabilized IPTWs, which were then normalized by dividing each participant's period-specific stabilized IPTW by their maximum stabilized IPTW. The normalization helped address extreme values by restricting the IPTW range from 0 to 1.[143] By weighting the pooled logistic regression using the IPTWs, the marginal effect (the effect if everyone *vs*. no one was exposed) of being exposed to NSAID use was estimated, controlling for the included co-variables.[144]

Figure 7. Schematic overview of the case-crossover design

Note: Patient #1 is exposed on the outcome date, patient #2 is exposed at the second reference point, and patient #3 is exposed neither on the outcome date nor any reference points and is dropped from the analysis
Abbreviation: NSAID, non-steroidal anti-inflammatory drug

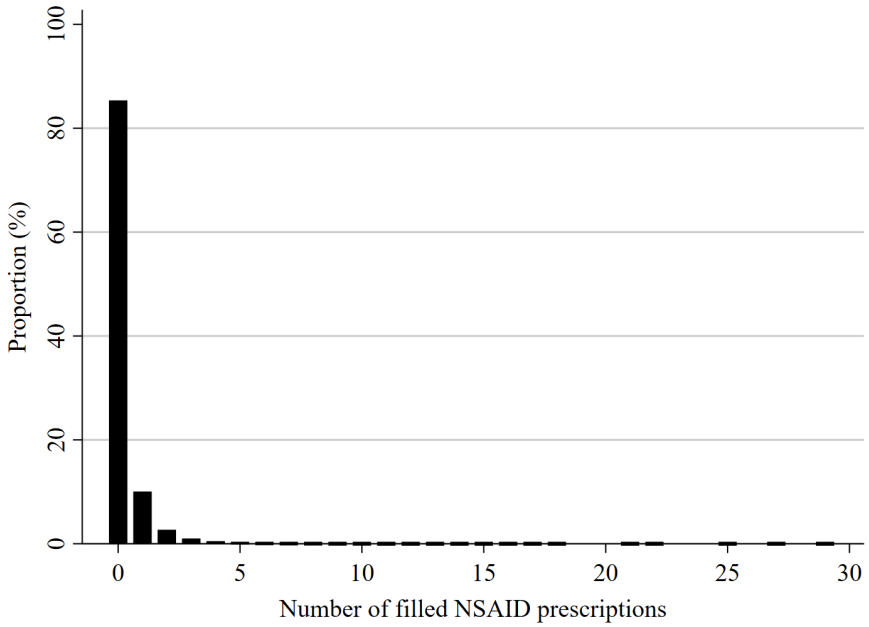
5. Results

The main findings from Studies I, II, and III are summarized below, while a comprehensive presentation of the results can be found in the Appendix.

5.1 Risk factors and NSAID use

Study I included 407,330 adult first-time responders to the Danish National Health Surveys of 2010, 2013, or 2017 who did not use NSAIDs at the time of their survey response. Among these individuals, 15% filled at least one prescription for an NSAID within one year of their survey response (Figure 8). Of these filled prescriptions, ibuprofen accounted for 70%, naproxen for 4.1%, diclofenac for 11%, and other NSAIDs for 15%.

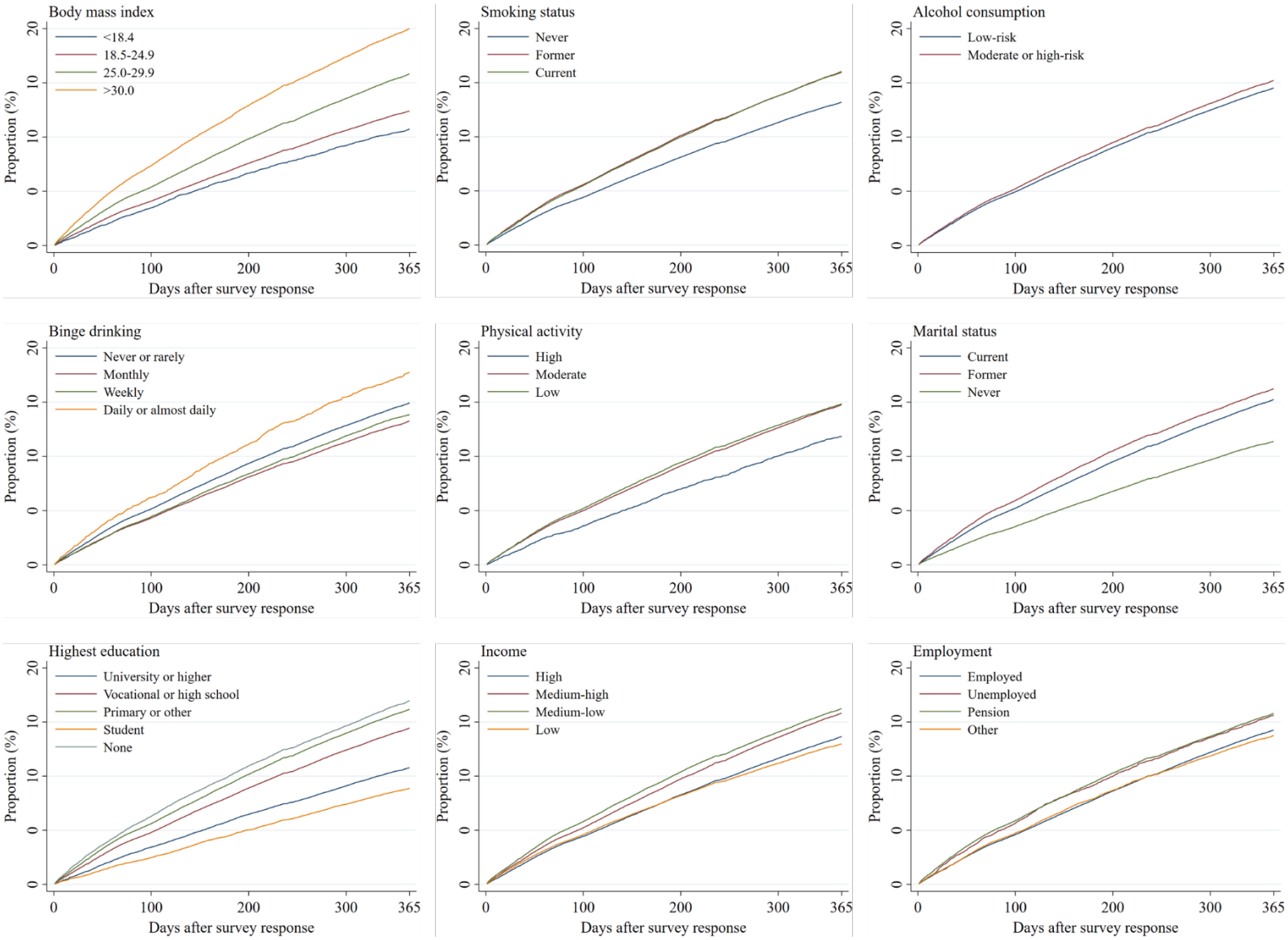
Figure 8. Number of filled NSAID prescriptions within one year after survey response



Abbreviation: NSAID, non-steroidal anti-inflammatory drug

The cumulative incidence of NSAID initiation was generally higher among individuals with modifiable and socioeconomic risk factors, except within subgroups of alcohol consumption, as shown in Figure 9.

Figure 9. Cumulative incidence of non-steroidal anti-inflammatory drug initiation within one year after survey response, by modifiable and socioeconomic cardiovascular risk factors



The results from the Cox proportional-hazards regression and the cumulative odds model were generally comparable (Table 7). The focus below is on the results from the cumulative odds model. We found the greatest differences in the amount of prescriptions filled among subgroups based on BMI, smoking status, marital status, level of education, and employment status (Table 7). Those with BMI ≥30.0 had a 69% increased risk (OR=1.69, 95% CI: 1.65–1.74) compared with those with BMI 18.5–24.9 kg/m2 and current smokers had a 25% increased risk (OR=1.25, 95% CI: 1.22–1.28) compared with never smokers. In addition, those never married had a 20% decreased risk (OR=0.80, 95% CI: 0.78–0.82) compared with those currently married, those with primary or other education had a 46% increased risk (OR=1.46, 95% CI: 1.41–1.52) compared with those with university or higher education, and the unemployed had a 16% increased risk (OR=1.16, 95% CI: 1.09–1.23) compared with the employed.

Table 7. Adjusted hazard ratios of NSAID initiation and adjusted odds ratios of filling one additional NSAID prescription within one year after survey response

Modifiable and socioeconomic risk factors	Hazard ratio (95% CI)	Odds ratio (95% CI)
Body mass index		
<18.5	0.87 (0.83–0.90)	0.84 (0.78–0.91)
18.5–24.9	1.00 (reference)	1.00 (reference)
25.0–29.9	1.23 (1.22–1.24)	1.31 (1.28–1.34)
≥30.0	1.48 (1.46–1.50)	1.69 (1.65–1.74)
Smoking status		
Never	1.00 (reference)	1.00 (reference)
Former	1.12 (1.11–1.13)	1.15 (1.12–1.17)
Current	1.20 (1.18–1.21)	1.25 (1.22–1.28)
Alcohol consumption		
Low-risk	1.00 (reference)	1.00 (reference)
Moderate or high-risk	1.05 (1.04–1.07)	1.10 (1.07–1.13)
Binge drinking		
Never or rarely	1.00 (reference)	1.00 (reference)
Monthly	0.99 (0.98–1.01)	0.95 (0.93–0.98)
Weekly	1.00 (0.98–1.02)	0.96 (0.92–1.00)
Daily or almost daily	1.10 (1.05–1.15)	1.13 (1.04–1.23)
Physical activity level		
High	1.00 (reference)	1.00 (reference)
Moderate	0.97 (0.94–1.00)	0.97 (0.91–1.03)
Low	0.90 (0.87–0.92)	0.84 (0.79–0.90)
Marital status		
Current	1.00 (reference)	1.00 (reference)
Former	0.96 (0.94–0.97)	0.91 (0.88–0.93)
Never	0.83 (0.81–0.84)	0.80 (0.78–0.82)
Highest education		
University or higher	1.00 (reference)	1.00 (reference)
Vocational or high school	1.21 (1.19–1.23)	1.27 (1.23–1.32)
Primary or other	1.33 (1.31–1.35)	1.46 (1.41–1.52)
Student	1.09 (1.06–1.13)	1.06 (1.00–1.13)
None	1.29 (1.26–1.32)	1.43 (1.37–1.50)
Income		
High	1.00 (reference)	1.00 (reference)
Medium-high	1.04 (1.03–1.06)	1.09 (1.06–1.12)
Medium-low	0.99 (0.98–1.00)	1.03 (1.00–1.06)
Low	0.85 (0.83–0.86)	0.82 (0.79–0.85)
Employment		
Employed	1.00 (reference)	1.00 (reference)
Unemployed	1.10 (1.06–1.13)	1.16 (1.09–1.23)
Pension	0.85 (0.83–0.86)	0.83 (0.81–0.86)
Other	0.98 (0.96–1.00)	1.02 (0.98–1.06)

Abbreviation: CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug

*Adjusted for sex, age, Quan-modified Charlson Comorbidity Index score, additional morbidities, drug use, and markers of lifestyle and socioeconomic position

5.2 Impact of risk factors on NSAID-associated cardiovascular risks

Study II included 22,834 adult first-time responders to the Danish National Health Surveys of 2010, 2013, or 2017 who did not use NSAIDs and experienced a cardiovascular event.

Our findings showed that compared with non-use, use of ibuprofen (OR=1.34, 95% CI: 1.23–1.46), naproxen (OR=1.48, 95% CI: 1.04–2.09), or diclofenac (OR=2.18, 95% CI: 1.72–2.78) was associated with increased cardiovascular risk (Table 8). We did not find any notable cardiovascular risk differences for any NSAID in subgroups according to modifiable and socioeconomic risk factors (Table 8).

Table 8. Self-controlled analyses of the association between ibuprofen, naproxen, or diclofenac and cardiovascular events (a composite of myocardial infarction, ischemic stroke, heart failure, and all-cause death), by modifiable and socioeconomic risk factors

Modifiable and socioeconomic risk factors	Ibuprofen	Naproxen	Diclofenac
	Odds ratio (95% confidence interval) comparing use with non-use		
Overall	1.34 (1.23–1.46)	1.48 (1.04–2.09)	2.18 (1.72–2.78)
Body mass index			
<18.5	1.55 (0.88–2.72)	*	1.67 (0.35–7.93)
18.5–24.9	1.37 (1.19–1.58)	0.89 (0.47–1.69)	2.38 (1.63–3.48)
25.0–29.9	1.34 (1.17–1.54)	1.54 (0.90–2.64)	2.05 (1.39–3.03)
≥30.0	1.17 (0.95–1.44)	2.18 (0.86–5.55)	1.96 (0.98–3.92)
Smoking status			
Never	1.38 (1.18–1.63)	1.57 (0.85–2.91)	2.67 (1.74–4.08)
Former	1.26 (1.09–1.46)	1.60 (0.83–3.08)	1.80 (1.21–2.68)
Current	1.37 (1.17–1.59)	1.27 (0.73–2.23)	2.09 (1.34–3.26)
Alcohol consumption			
Low-risk	1.25 (1.13–1.39)	1.46 (0.96–2.24)	2.05 (1.54–2.74)
Moderate or high-risk	1.60 (1.34–1.90)	1.48 (0.78–2.82)	2.33 (1.39–3.91)
Physical activity level			
High	1.91 (1.04–3.52)	*	*
Moderate	1.37 (1.23–1.51)	1.23 (0.82–1.85)	1.66 (1.22–2.25)
Low	1.23 (1.02–1.47)	2.19 (1.03–4.63)	3.45 (2.14–5.55)
Marital status			
Current	1.37 (1.24–1.53)	1.68 (1.09–2.59)	2.21 (1.62–3.02)
Former	1.31 (1.10–1.57)	0.65 (0.26–1.64)	1.96 (1.25–3.09)
Never	1.08 (0.80–1.46)	0.88 (0.31–2.45)	3.25 (1.36–7.75)
Highest education			
University or higher	1.19 (0.85–1.68)	0.36 (0.06–2.14)	8.50 (2.42–29.9)
Vocational or high school	1.33 (1.12–1.59)	0.92 (0.42–2.02)	2.61 (1.49–4.58)
Primary or other	1.41 (1.25–1.60)	2.16 (1.28–3.63)	2.02 (1.40–2.92)
Student	0.92 (0.29–2.92)	*	*
None	1.22 (0.99–1.51)	1.82 (0.82–4.06)	1.73 (1.06–2.81)
Income			
High	1.36 (1.08–1.69)	0.53 (0.15–1.82)	2.55 (1.29–5.02)
Medium-high	1.24 (1.03–1.50)	1.53 (0.66–3.56)	2.13 (1.17–3.89)
Medium-low	1.34 (1.16–1.56)	2.52 (1.34–4.76)	2.55 (1.66–3.94)
Low	1.39 (1.19–1.62)	1.31 (0.77–2.24)	1.83 (1.26–2.67)
Employment			
Employed	1.25 (1.09–1.44)	1.16 (0.62–2.16)	2.00 (1.27–3.15)
Unemployed	1.37 (0.77–2.41)	*	*
Pension	1.36 (1.21–1.52)	1.73 (1.12–2.69)	1.91 (1.41–2.59)
Other	0.98 (0.58–1.67)	*	3.80 (1.07–13.6)

*Not applicable because of few events

In the comparison of individual NSAIDs, use of ibuprofen and naproxen was associated with comparable cardiovascular risks (OR=1.10, 95% CI: 0.77–1.57 comparing naproxen with ibuprofen), while use of diclofenac was associated with a higher cardiovascular risk compared with use of ibuprofen (OR=1.62, 95% CI: 1.25–2.08) or naproxen (OR=1.47, 95% CI: 0.97–2.24; Table 9). No notable differences in cardiovascular risk were observed within subgroups according to modifiable and socioeconomic risk factors, neither in the

comparison of naproxen with ibuprofen nor in the comparison of diclofenac with either ibuprofen or naproxen (Table 9).

Table 9. Self-controlled analyses comparing the association between individual NSAIDs and cardiovascular events (a composite of myocardial infarction, ischemic stroke, heart failure, and all-cause death), by modifiable and socioeconomic risk factors

Modifiable and socioeconomic risk factors	Naproxen vs. ibuprofen	Diclofenac vs. ibuprofen	Diclofenac vs. naproxen
	Odds ratio (95% confidence interval) comparing individual NSAIDs		
Overall	1.10 (0.77–1.57)	1.62 (1.25–2.08)	1.47 (0.97–2.24)
Body mass index			
<18.5	*	1.08 (2.05–5.66)	*
18.5–24.9	0.65 (0.34–1.24)	1.73 (1.15–2.59)	2.67 (1.27–5.62)
25.0–29.9	1.14 (0.65–1.99)	1.52 (1.01–2.30)	1.34 (0.69–2.60)
≥30.0	1.84 (0.71–4.79)	1.59 (0.78–3.26)	0.87 (0.27–2.76)
Smoking status			
Never	1.12 (0.59–2.12)	1.87 (1.19–2.93)	1.66 (0.79–3.52)
Former	1.25 (0.64–2.44)	1.41 (0.93–2.15)	1.13 (0.52–2.42)
Current	0.94 (0.53–1.67)	1.54 (0.96–2.46)	1.64 (0.80–3.35)
Alcohol consumption			
Low-risk	1.16 (0.75–1.79)	1.61 (1.18–2.18)	1.39 (0.83–2.32)
Moderate or high-risk	0.94 (0.48–1.82)	1.47 (0.86–2.54)	1.58 (0.69–3.59)
Physical activity level			
High	*	*	*
Moderate	0.89 (0.59–1.36)	1.21 (0.88–1.67)	1.35 (0.81–2.25)
Low	1.76 (0.82–3.82)	2.71 (1.63–4.49)	1.54 (0.63–3.72)
Marital status			
Current	1.21 (0.78–1.89)	1.60 (1.15–2.22)	1.32 (0.77–2.25)
Former	0.50 (0.19–1.27)	1.46 (0.90–2.38)	2.95 (1.06–8.23)
Never	0.81 (0.28–2.37)	3.01 (1.20–7.55)	3.71 (0.96–14.3)
Highest education			
University or higher	0.30 (0.05–1.81)	5.56 (1.68–18.3)	18.7 (2.27–154)
Vocational or high school	0.69 (0.31–1.55)	1.97 (1.09–3.54)	2.83 (1.08–7.43)
Primary or other	1.51 (0.88–2.58)	1.41 (0.96–2.08)	0.94 (0.50–1.77)
Student	*	*	*
None	1.49 (0.65–3.40)	1.41 (0.83–2.39)	0.95 (0.37–2.42)
Income			
High	0.38 (0.11–1.35)	1.85 (0.90–3.77)	4.84 (1.18–19.9)
Medium-high	1.21 (0.51–2.88)	1.64 (0.88–3.05)	1.35 (0.48–3.79)
Medium-low	1.87 (0.98–3.60)	1.90 (1.20–3.00)	1.01 (0.47–2.18)
Low	0.94 (0.54–1.65)	1.32 (0.88–1.98)	1.40 (0.73–2.69)
Employment			
Employed	0.91 (0.48–1.73)	1.55 (0.97–2.49)	1.70 (0.79–3.66)
Unemployed	*	*	*
Pension	1.27 (0.81–2.00)	1.40 (1.01–1.94)	1.10 (0.65–1.88)
Other	*	3.86 (0.97–15.3)	*

Abbreviation: NSAID, non-steroidal anti-inflammatory drug

*Not applicable because of few events

5.3 Impact of glycemic regulation on NSAID-associated cardiovascular risks

Study III included 103,308 adults who had a first-time HbA1c measurement ≥48 mmol/mol between 2012 and 2020, who did not use NSAIDs and did not have a previous cardiovascular disease diagnosis. Among these individuals, 57% had well-regulated diabetes (HbA1c <53 mmol/mol) and 43% had less well-regulated diabetes (HbA1c ≥53 mmol/mol) at the time of their first elevated HbA1c measurement. At this time, 19% were using statins, 25% among those with well-regulated type 2 diabetes and 11% among those with less well-regulated type 2 diabetes. The number of HbA1c measurements during follow-up ranged from 1 to 83, with a median of 8 and an interquartile range of 4 to 14.

We found that use of ibuprofen (HR=1.43, 95% CI: 1.28–1.60) and diclofenac (HR=2.52, 95% CI: 1.83–3.48) were associated with a higher rate of cardiovascular events, whereas use of naproxen was not (HR=1.18, 95% CI: 0.68–2.04; Table 10). After stratifying by HbA1c level, we found that use of ibuprofen was associated with a higher rate of cardiovascular events both in well-regulated (HR=1.53, 95% CI: 1.34–1.75) and less well-regulated patients (HR=1.24, 95% CI: 1.00–1.53; Table 10). The same was found for diclofenac with comparable increased rates of cardiovascular events in well-regulated (HR=2.40, 95% CI: 1.62–3.56) and less well-regulated patients (2.89, 95% CI: 1.65–5.04; Table 10). Naproxen use was not associated with an increased rate of cardiovascular events in either well-regulated (HR=1.14, 95% CI: 0.59–2.21) or less well-regulated patients (HR=1.30, 95% CI: 0.49–3.49; Table 10).

Table 10. Association between use of ibuprofen, naproxen, or diclofenac and cardiovascular events (a composite of myocardial infarction, ischemic stroke, congestive heart failure, atrial fibrillation, and all-cause death) in patients with type 2 diabetes comparing use with non-use, by hemoglobin A1c level

Non-steroidal anti-inflammatory drug	Hemoglobin A1c	Weighted* hazard ratio (95 % confidence interval)
Ibuprofen	Overall	1.43 (1.28–1.60)
	<53 mmol/mol	1.53 (1.34–1.75)
	≥53 mmol/mol	1.24 (1.00–1.53)
Naproxen	Overall	1.18 (0.68–2.04)
	<53 mmol/mol	1.14 (0.59–2.21)
	≥53 mmol/mol	1.30 (0.49–3.49)
Diclofenac	Overall	2.52 (1.83–3.48)
	<53 mmol/mol	2.40 (1.62–3.56)
	≥53 mmol/mol	2.89 (1.65–5.04)

*Inverse probability of treatment weighted by sex, age, the Danish Comorbidity Index for Acute Myocardial infarction restricted to non-cardiovascular diseases (rDANCAMI) score, and drug use

6. Discussion

6.1 Summary of main findings

In Study I, 'Risk factors and NSAID use', we found that modifiable and socioeconomic risk factors such as high BMI, current smoking, moderate or high-risk alcohol consumption, frequent binge drinking, low education level, and unemployment were related to a higher rate of initiating NSAID treatment and subsequent NSAID use.

In Study II, 'Impact of risk factors on NSAID-associated cardiovascular risks', we found that, among people without a prior diagnosis of cardiovascular disease, the cardiovascular risks associated with NSAID use did not vary notably among subgroups according to modifiable and socioeconomic risk factors. Compared with use of ibuprofen or naproxen, use of diclofenac was associated with larger risk, both overall and among people with BMI 25.0–29.9, current smokers, those with moderate or high-risk alcohol consumption, those who were physical inactive, those with short or no education, and those with low income.

In Study III, 'Impact of glycemic regulation on NSAID-associated cardiovascular risks' we found that, among patients with type 2 diabetes without a previous diagnosis of myocardial infarction, ischemic stroke, congestive heart failure, or atrial fibrillation or flutter, use of ibuprofen or diclofenac, but not naproxen, was associated with increased rate of cardiovascular events. This association was not influenced by glycemic regulation as measured by HbA1c.

6.2 Previous literature

6.2.1 Study I: Risk factors and NSAID use

Our results showing increased NSAID use in individuals with modifiable and socioeconomic risk factors contradict those from a previous study showing that individuals with a socioeconomic disadvantage (estimated via the Index of Multiple Deprivation)[145] were prescribed less NSAIDs than individuals with a socioeconomic advantage (OR=0.37, 95% CI: 0.17–0.84).[49] The reason for increased NSAID use associated with modifiable and socioeconomic risk factors might be due their connection with pain-related conditions such as rheumatoid arthritis, osteoarthritis, osteoporosis, and back pain.[87, 103, 104]

Our findings suggest that modifiable and socioeconomic risk factors can confound the association between NSAID use and cardiovascular events in observational studies if not controlled for. However, it is questionable if controlling for such risk factors will reduce confounding bias in observational studies examining NSAID-associated cardiovascular risks for three reasons. First, age and sex seem to be the main drivers of confounding bias in many settings.[146] Second, controlling for modifiable and socioeconomic risk factors have shown minor impact on the association between NSAID use and myocardial infarction.[88, 89] One study found that if not controlled for, BMI, smoking, education, income, and aspirin use only resulted in little bias towards the null of the association between NSAID use and myocardial infarction;[89] this when comparing use of selective COX-2 inhibitors with non-selective NSAIDs (-1.56%), non-use (-0.54%), naproxen (-1.86%), or rofecoxib (-3.15%).[89] Another study found that a logistic regression model conditioning on age, sex, comorbidity burden, and drug use and another logistic regression model further conditioning on BMI, smoking status, exercise level, and alcohol use generated comparable results for the association between NSAID use and myocardial infarction for use of selective COX-2 inhibitors (OR=1.07, 95% CI: 0.52–2.18 *vs*. OR=1.08, 95% CI: 0.52–2.22) and conventional NSAIDs (OR=0.93, 95% CI: 0.77–1.12 *vs*. OR=0.89, 95% CI: 0.73–1.09).[88] However, this study had limitations such as selection bias (only 24% of cases and 8% of controls returned the behavior questionnaire) and no baseline differences in modifiable and socioeconomic

risk factors between cases and controls, thereby eliminating their potential as confounders.[88] Third, the association between modifiable and socioeconomic risk factors and NSAID use was in our study found to be modest. Therefore, if not controlled for, the potential confounding bias introduced by these factors would also be modest.[147] Nevertheless, because the association between NSAID use and cardiovascular events reported in previous observational studies is also modest,[7, 12] modifiable and socioeconomic risk factors still have the potential to introduce critical confounding bias.[147] As the potential confounding bias cannot be estimated a priori, we recommend obtaining information on modifiable and socioeconomic risk factors when examining NSAID-associated cardiovascular risks.

6.2.2 Study II: Impact of risk factors on NSAID-associated cardiovascular risks

Our findings are the first to describe the cardiovascular risks associated with NSAID use in individuals with modifiable and socioeconomic risk factors, but without manifest cardiovascular disease. According to current guidelines,[14] physicians should consider an individual's cardiovascular risk profile before prescribing NSAIDs, also for individuals without manifest cardiovascular disease. Yet, it seems that NSAIDs are frequently prescribed to individuals with modifiable and socioeconomic risk factors.[87] For example, in Danish patients with a first-time diagnosis of a cardiovascular disease, hypertension has been associated with a 3% increased risk and obesity with a 32% increased risk of filling at least one NSAID prescription within a year.[87] Whether similar associations exist among individuals without manifest cardiovascular disease is unknown, but it seems likely that the baseline cardiovascular risk would be considered less among such individuals.

Our findings suggest that caution should be exercised when prescribing NSAIDs to all individuals, and perhaps especially to individuals with modifiable and socioeconomic risk factors, as comparable *relative* risk increases translate into higher *absolute* risk increases.

6.2.3 Study III: Impact of glycemic regulation on NSAID-associated cardiovascular risks

Our results showing increased cardiovascular risk associated with NSAID use in patients with type 2 diabetes are in agreement with those from a previous study showing a 20% increased rate of myocardial infarction and ischemic stroke (incidence rate ratio=1.21, 95% CI: 1.17–1.26) associated with NSAID use in patients with type 2 diabetes.[50] Our findings that HbA1c level did not impact this association align with those from Study II, suggesting comparable relative cardiovascular risk increases associated with NSAID use in low and high-risk individuals. Despite current guidelines,[14] it seems that NSAIDs are still frequently prescribed to patients with type 2 diabetes.[87] For example, in Danish patients with a first-time hospital diagnosis of a cardiovascular disease, type 2 diabetes has been associated with a 6% increased risk of filling at least one NSAID prescription within a year.[87]

Our findings indicate that NSAIDs should be prescribed carefully to all patients with type 2 diabetes, given their already increased cardiovascular risk.[39] Perhaps particular care should be taken when prescribing NSAIDs to those with dysregulated type 2 diabetes, due to their further elevated cardiovascular risk.[33, 48]

6.3 Limitations

6.3.1 Random error

Random error describes the differences between the *observed* and the *true* value due to chance.[148] All things else being equal, increasing sample size decreases random error (*i.e.*, increases precision).[148, 149] Thus, the

rather large sample sizes in all studies increased precision, but the low exposed time at the time of the outcome in Studies II and III decreased precision.

The size of random error is often described with a CI surrounding the estimate of interest. A CI presents the range that with a certain probability would contain the *true* value if the study was replicated an unlimited amount of time (given true model specification and no bias present).[148] We used a 95% confidence level in all analyses. Because of the many analyses in Studies I and II, one could argue that we should have used a higher confidence level to lower the risk of false positive results (*i.e.*, type I errors).[150, 151] We decided not to increase the confidence level because this would have increased the risk of false negative results (*i.e.*, type II errors), thereby further limiting interpretation.

In alignment with recommendations, we restrained from reporting p-values.[152-154] Because a p-value merges information on the effect size and the precision,[148] a CI is more informative given that it is not just interpreted as significant or non-significant.[148]

6.3.2 Selection bias

The universal tax-financed health care provided by the Danish healthcare system[114] as well as the virtually complete long-term follow-up provided by the Danish Civil Registration System[115] reduced the risk of selection bias in all studies.

The Cox proportional-hazards regression used in Study I has a built-in selection bias caused by unevenly depletion of susceptible individuals across exposure groups.[141] The degree of this uneven depletion of susceptible individuals grows with the incidence of the competing risk and the length of follow-up. Because the Study I cohort consisted of relatively healthy individuals (a representative sample of the Danish population capable of completing a multi-questionnaire survey) and because the follow-up was at most nine years and eight months (from May 1, 2010 to December 31, 2019), few individuals experienced the competing event of death, likely limiting the degree of bias on the relative estimates. However, because of a relative healthy cohort, the absolute estimates, such as cumulative incidence proportions of NSAID initiators in Study I, might be lower than in the general population.

6.3.3 Information bias

6.3.3.1 Exposure

The self-reported answers to the Danish National Health Surveys[116] generated the potential of exposure misclassification. Because Danish registries obtain data prospectively, individuals were unaware of their outcome status at the time of answering the survey. Thus, the potential exposure misclassification in Study I is likely non-differential, thereby biasing the effect estimates towards a null association[148] (given independent misclassification).[155] However, because of polytomous exposure groups, bias in an unpredicted direction in the middle subgroups cannot be ruled out.[156, 157]

Defining NSAID use via filled prescriptions generated three major issues. First, due to the absence of daily dose or treatment duration in the Danish National Prescription Registry,[121] we had to estimate NSAID exposure length on existing knowledge. Instead of using a fixed exposure window, we determined exposure length by considering the number and the strength of the tablets from the filled prescriptions.[158, 159] We calculated exposure lengths in various ways, including the full and half defined daily dose when used to treat pain or fever according to Danish guidelines, and using two or three daily tablets no matter the dose. We also used different gap lengths (14 days, 30 days, and 60 days) because higher gap lengths generate longer treatment durations.[160] Neither approach is likely perfect in capturing the true exposure length, leading to some expo-

sure misclassification, which would likely be non-differential and thereby generate bias towards a null association. After changing the exposure definition and the gap length, the results from Studies II and III did not change much, supporting the robustness of our findings. Second, as the Danish National Prescription Registry only contains information from filled prescriptions from Danish pharmacies,[121] some individuals classified as NSAID non-users could have been over-the-counter ibuprofen users or in-hospital NSAID users. Such exposure misclassification would also likely be non-differential, only generating minor bias towards a null association because of rare exposure to NSAIDs.[161] Furthermore, during the study periods, ibuprofen in packages of 20 tablets of 200 mg per tablet was the only NSAID available over-the-counter,[19] and over-the-counter ibuprofen sales only accounts for between 25% to 33% of total ibuprofen sales in Denmark.[19] As a result, it has been shown that the proportion of *true* ibuprofen users wrongly classified as non-users in Denmark is too small to substantially bias associations between NSAID use and cardiovascular events.[162] Third, we lacked information on the adherence after a filled NSAID prescription. No study has examined this adherence or the impact of non-adherence on the effect estimates when examining NSAID-associated cardiovascular risks. The potential exposure misclassification generated from non-adherence in Studies II and III would likely be non-differential, only biasing the effect estimates a little towards a null association due to the short time wrongly defined as exposed.[148] Because the bias generated from exposure misclassification in Studies II and III all likely would be towards a null association, it would not be able to explain the observed associations of increased cardiovascular risks associated with NSAID use.

6.3.3.2 Outcome

The misclassification issues regarding defining NSAID use via filled prescriptions described above also apply to the Study I outcomes.

Any potential outcome misclassification would likely be non-differential because of the prospective collection of data. Non-differential outcome misclassification solely due to lack of *sensitivity* (*i.e.*, false negatives) would only result in minor bias of ORs and HRs towards a null association, given the outcome is rare.[148] It is consequently of minor concern that the completeness of the cardiovascular outcomes in the Danish National Patient Registry[119] has not been examined. Thus, lack of *specificity* (*i.e.*, false positives) is the main concern regarding non-differential outcome misclassification, since this to a larger degree can bias effect estimates towards a null association.[148] Registration of all cardiovascular outcomes has been validated within the Danish National Patient Registry with positive predictive values of 97% for myocardial infarction,[163] 88% for ischemic stroke,[164] 76% for congestive heart failure,[163] and 95% for atrial fibrillation or flutter.[163] Hence, only false-positive ischemic strokes and congestive heart failures seem to be a concern. The Danish Civil Registration System contains almost complete information on the date of death or emigration,[115] so misclassification of vital status is negligible. No study has examined the specificity of the cause of death in the Danish Register of Causes of Death.[125] The autopsy rate in Denmark is estimated to less than 10%,[125] and the majority of death causes are therefore based on a physician's conclusion — often the youngest, least experienced physician on duty. For these reasons, the validity of the death cause can be questioned. To circumvent this issue, we focused on all-cause rather than cardiovascular death, and only used the main underlying cause, and not the contributory causes, of death to define cardiovascular death in Study III.

6.3.3.3 Co-variables

The misclassification issues regarding the self-reported answers on modifiable and socioeconomic cardiovascular risk factors described above also apply to the Study II subgroup definitions.

To estimate a patient's current HbA1c level, we updated an individual's HbA1c whenever a new measurement was taken. It is possible that a patient changed in HbA1c level between two measurements, thereby potentially being wrongly classified until an update was made. However, because HbA1c reflects blood glucose levels during the past 120 days,[39] this potential subgroup misclassification in Study III is likely less than if other diagnostic tests had been used.

We used the Quan-modified Charlson Comorbidity Index[126] and the Danish Comorbidity Index for Acute Myocardial infarction restricted to non-cardiovascular diseases (rDANCAMI)[127] to control for comorbidity burden. Registration of the Charlson Comorbidity Index comorbidities has been validated within the Danish National Patient Registry with positive predictive values of at least 94% for all comorbidities (except for 82% for diabetes mellitus with chronic complications),[165] but registration of several rDANCAMI comorbidities has not. Also, comorbidities such as obesity, alcohol and drug abuse, affective disorder, chronic pulmonary disease, and hypertension might not have a record within the Danish National Patient Registry if they are treated solely by a general practitioner.[119] For example, the completeness of obesity within the Danish National Patient Registry has been estimated to only 11%.[166] To circumvent this issue, we used fillings of relevant prescription drugs as disease proxies for affective disorder, chronic pulmonary disease, diabetes, and hypertension. However, some misclassification may persist. All included drugs were only available via prescription during the study periods. No study has examined the adherence after a filled prescription to the included drugs. A significant non-adherence would result in many false positives. In addition, the number of comorbidities might be higher among individuals with frequent healthcare encounters, generating uneven chances of receiving a comorbidity diagnosis between individuals.[167] The potential comorbidity and drug misclassification would likely be non-differential, resulting in only partial control for these co-variables and thereby to controlled and crude effect estimates closer together than otherwise.[161, 168]

6.3.4 Confounding bias

6.3.4.1 Confounding by indication

Confounding by indication occurs when an observed association between exposure and outcome is in fact (partly or fully) an association between exposure *indication* and outcome.[169] The indication for NSAID use, *e.g.*, inflammatory disease,[170] could cause confounding by indication in Studies II and III. Unfortunately, information on treatment indication was not available.[121] To limit confounding by indication in pharmacoepidemiology, it is good practice to use an active comparator drug design,[171] *i.e.*, comparing the drug of interest with another drug used for the same indication, rather than comparing drug use with non-use. In Study II, we compared use of the NSAIDs ibuprofen, naproxen, or diclofenac with non-use and between each other individually. In Study III, we did not compare the individual NSAIDs with acetaminophen (paracetamol) because recent studies suggest that acetaminophen also increases the cardiovascular risk[172] and inhibit COX enzymes in a manner similar to NSAIDs.[173]

6.3.4.2 Unmeasured confounding

Study III was limited by the lack of information on modifiable and socioeconomic risk factors. However, the impact of lack of such information on the association between NSAID use and cardiovascular events seems to be minor.[88, 89] Also, because the Study III cohort consisted of patients with type 2 diabetes, the differences in modifiable and socioeconomic risk factors between patients might be lower than if the cohort had also consisted of individuals from the general population.

The potential misclassification of comorbidities and drug use described above could result in residual confounding. However, in many situations, after controlling for age and sex, further controlling for a comorbidity score does not seem to reduce confounding further.[146] The reason for this little (if any) benefit of controlling for a comorbidity score could be the oversimplistic estimation of comorbidity burden when using registry data.[146]

6.3.5 Generalization

In the following, there will differentiated between *generalizability*, *i.e.*, whether results generalize to the target population, and *transportability*, *i.e.*, whether results apply to populations other than the target population.[138]

The cohorts of Studies I and II were sampled from nationwide surveys send to a representative sample of the Danish population,[116] increasing generalization to the entire Danish population. However, the survey response rates ranged from 50% to 60%,[116] potentially limiting generalizability if responders and non-responders differed in characteristics important to the association examined in Studies I and II. For example, in 2010, the response rate was 56% in males *vs*. 63% in females. In Study I, we tried to circumvent this limitation by weighing our analyses by age and sex. Yet, unknown differences between responders and non-responders might still limit generalizability. Also, differences between countries in mortality due to smoking, obesity, and high alcohol consumption as well as low income, short education, and unemployment might limit transportability.[42]

In Study III, we used an HbA1c measurement ≥48 mmol/mol to identify patients with type 2 diabetes. Thus, naturally only individuals with an HbA1c measurement in the first place were included in the study. Previous research suggests that around 33% of adult patients with type 2 diabetes are undiagnosed.[45] Hence, we likely missed several individuals with undiagnosed type 2 diabetes. Also, the information on HbA1c was first nationwide from 2015[123] and only regional between 2012 and 2014.[122] However, because of a homogenous Danish population — regarding demographic characteristics, socioeconomic position, use of healthcare services, and use of prescription drugs[174] as well as genetics[175] — the results might still generalize to all Danish patients with type 2 diabetes. This homogeneity might limit the transportability of the results to other countries with heterogenous populations though.

Individuals using NSAIDs via prescription and over-the-counter might differ. Consequently, the results from Studies II and III might not transport to countries with larger over-the-counter NSAID sales than in Denmark,[19] such as the United States.[176]

The treatment of type 2 diabetes might differ between countries with free access to healthcare, such as in Denmark,[114] and more self-paid healthcare, such as in the United States. Also, type 2 diabetes complications depend on HbA1c level,[33, 48] and higher BMI is associated with higher HbA1c level.[177] Thus, countries with more individuals with high BMI than in Denmark (*e.g.*, several countries in South America),[178] might have more patients with dysregulated type 2 diabetes. For these reasons, the Study III results might not transport to such countries.

6.3.6 Composite outcomes

Use of composite outcomes increased the precision and thereby allowed for comparisons of individual drugs and subgroups of patients.[148] It is important to notice that interpretation of composite outcomes can be difficult if the individual components differ in their clinical importance, severity, number, and/or association with the exposure of interest.[179-181] To increase transparency, we therefore also examined the association between NSAID use and the individual components of the composite outcome.

7. Conclusions and perspectives

This dissertation has improved the understanding of the association between NSAID use and cardiovascular events in individuals with modifiable and socioeconomic risk factors for cardiovascular disease.

In Study I, 'Risk factors and NSAID use', we found that several modifiable and socioeconomic risk factors were related to a higher rate of initiating NSAID treatment and subsequent NSAID use. Our findings suggest that such factors should be considered potential confounders in observational studies examining the cardiovascular risks associated with NSAID use.

In Study II, 'Impact of risk factors on NSAID-associated cardiovascular risks', we found that, among people without a prior diagnosis of cardiovascular disease, the cardiovascular risks associated with NSAID use did not vary notably among subgroups according to modifiable and socioeconomic risk factors. Compared with use of ibuprofen or naproxen, use of diclofenac was associated with larger risk, both overall and in several subgroups with increased cardiovascular risk. Our findings suggest that caution should be exercised when prescribing NSAIDs to all individuals, and perhaps especially to individuals with modifiable and socioeconomic risk factors, due to their higher baseline risk.

In Study III, 'Impact of glycemic regulation on NSAID-associated cardiovascular risks', we found that, among patients with type 2 diabetes without a previous diagnosis of myocardial infarction, ischemic stroke, congestive heart failure, or atrial fibrillation or flutter, use of ibuprofen or diclofenac, but not naproxen, was associated with increased rate of cardiovascular events. This association was not influenced by glycemic regulation. Our findings suggest that NSAIDs should be prescribed carefully to all patients with type 2 diabetes, but perhaps particularly to patients with dysregulated type 2 diabetes, given their increased baseline risk.

8. Unanswered questions

Important questions that remain unanswered include the impact of other modifiable risk factors, such as dyslipidemia and hypertension, on the cardiovascular risks associated with NSAID use. The importance of prescribing NSAIDs with caution to high-risk individuals, would be further emphasized should similar relative risk increases be found among individuals with high and low cholesterol levels and high and low blood pressure.

It would also be important to study the impact of other biomarkers (*e.g.*, pro-inflammatory proteins and cholesterol) and treatments (*e.g.*, statins and antihypertensives) on the association between NSAID use and cardiovascular events in patients with type 2 diabetes.[182] Gaining knowledge about this impact could lead to revised guidelines for NSAID use in patients with type 2 diabetes.

9. Summary

Through three studies, we examined (1) the association between modifiable and socioeconomic cardiovascular risk factors and use of NSAIDs, (2) the impact of such risk factors on the association between use of NSAIDs and cardiovascular events among individuals without manifest cardiovascular disease, and (3) the impact of glycemic regulation on the association between use of NSAIDs and cardiovascular events among patients with type 2 diabetes.

In Study I, we found that modifiable and socioeconomic risk factors such as high BMI, current smoking, moderate or high-risk alcohol consumption, frequent binge drinking, low education level, and unemployment were related to a higher rate of initiating NSAID treatment and subsequent NSAID use.

In Study II, we found that, among people without a prior diagnosis of cardiovascular disease, the cardiovascular risks associated with NSAID use did not vary notably among subgroups defined by modifiable and socioeconomic risk factors. Compared with use of ibuprofen or naproxen, use of diclofenac was associated with larger risk, both overall and in people with BMI 25–29.9, current smokers, those with moderate or high-risk alcohol consumption, those who are physical inactive, those with short or no education, and those with low income. We concluded that caution should be exercised when prescribing NSAIDs to all individuals, and perhaps especially to individuals with modifiable and socioeconomic risk factors, due to their higher baseline risk.

In Study III, we found that, among patients with type 2 diabetes without a previous diagnosis of myocardial infarction, ischemic stroke, congestive heart failure, or atrial fibrillation or flutter, use of ibuprofen or diclofenac, but not naproxen, was associated with increased rate of cardiovascular events. This association was not influenced by glycemic regulation as measured by HbA1c. We concluded that NSAIDs should be prescribed carefully to all patients with type 2 diabetes, but perhaps particularly to patients with dysregulated type 2 diabetes, given their increased baseline risk.

10. Dansk resumé (Danish summary)

Igennem tre studier har vi undersøgt, (1) om modificerbare og socioøkonomiske risikofaktorer for hjertekarsygdom var forbundet med øget brug af ikke-steroidholdige anti-inflammatoriske lægemidler (NSAID), (2) om sådanne risikofaktorer havde indflydelse på sammenhængen imellem brug af NSAID og risikoen for hjertekarsygdom, og (3) om blodsukkerreguleringen hos patienter med type 2 diabetes havde indflydelse på sammenhængen imellem brug af NSAID og risikoen for hjertekarsygdom.

I Studie I fandt vi, at modificerbare og socioøkonomiske risikofaktorer såsom høj BMI, rygning, moderat eller høj-risiko alkoholforbrug, hyppigt indtag af minimum fem alkoholiske genstande, lavt uddannelsesniveau og arbejdsløshed var forbundet med øget brug af NSAID. Vi konkluderede, at modificerbare og socioøkonomiske risikofaktorer bør overvejes som mulige årsags-forvekslere i observationelle studier, der undersøger sammenhængen imellem brug af NSAID og hjertekarsygdom.

I Studie II fandt vi, at hos personer uden tidligere hjertekarsygdom var den relative risikoforøgelse for hjertekarsygdom forbundet med brug af NSAID sammenlignelig for personer med og uden modificerbare og socioøkonomiske risikofaktorer. Vi konkluderede, at NSAID bør udskrives varsomt til alle personer men måske især til dem med modificerbare og socioøkonomiske risikofaktorer grundet deres allerede øgede risiko.

I Studie III fandt vi, at hos patienter med type 2 diabetes uden tidligere hjertekarsygdom var brug af NSAID typerne 'ibuprofen' og 'diclofenac' forbundet med en øget risiko for hjertekarsygdom, hvorimod brug af typen 'naproxen' ikke var. Denne sammenhæng afhang ikke væsentligt af, om patienterne havde et velreguleret eller mindre velreguleret blodsukker niveau. Vi konkluderede, at NSAID bør udskrives varsomt til alle patienter med type 2 diabetes men måske især til dem med mindre velreguleret blodsukker grundet deres allerede øgede risiko.

11. References

1. Grosser T, Yu Y and Fitzgerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annual review of medicine* 2010; 61: 17-33. 2010/01/12.
2. García Rodríguez LA and Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet (London, England)* 1994; 343: 769-772.
3. Rao P and Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. *J Pharm Pharm Sci* 2008; 11: 81s-110s. 20080920.
4. Wolfe MM, Lichtenstein DR and Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *The New England journal of medicine* 1999; 340: 1888-1899.
5. Bonnesen K and Schmidt M. Re-categorization of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) according to clinical relevance: Abandoning the ´traditional NSAID´ terminology. *The Canadian journal of cardiology* 2021 2021/06/29.
6. McGettigan P and Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011; 8: e1001098. 20110927.
7. Martín Arias LH, Martín González A, Sanz Fadrique R and Vazquez ES. Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs and Classical and Selective Cyclooxygenase-2 Inhibitors: A Meta-analysis of Observational Studies. *Journal of clinical pharmacology* 2019; 59: 55-73. 2018/09/12.
8. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ (Clinical research ed)* 2011; 342: c7086. 2011/01/13.
9. Gunter BR, Butler KA, Wallace RL, Smith SM and Harirforoosh S. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. *J Clin Pharm Ther* 2017; 42: 27-38. 20161226.
10. Scott PA, Kingsley GH and Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008; 10: 1102-1107. 20080829.
11. Chokesuwattanaskul R, Chiengthong K, Thongprayoon C, et al. Nonsteroidal anti-inflammatory drugs and incidence of atrial fibrillation: a meta-analysis. *Qjm* 2020; 113: 79-85.
12. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacepidemiol Drug Saf* 2013; 22: 559-570. 2013/04/26.
13. Aw TJ, Haas SJ, Liew D and Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Archives of internal medicine* 2005; 165: 490-496. 20050214.
14. Schmidt M, Lamberts M, Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J* 2016; 37: 1015-1023. 2016/03/18.
15. Kristensen KB, Karlstad Ø, Martikainen JE, et al. Nonaspirin Nonsteroidal Antiinflammatory Drug Use in the Nordic Countries from a Cardiovascular Risk Perspective, 2000-2016: A Drug Utilization Study. *Pharmacotherapy* 2019; 39: 150-160. 20190208.
16. Fassio V, Aspinall SL, Zhao X, et al. Trends in opioid and nonsteroidal anti-inflammatory use and adverse events. *Am J Manag Care* 2018; 24: e61-e72. 20180301.
17. Hwang AY, Dave CV and Smith SM. Use of Prescription Medications That Potentially Interfere With Blood Pressure Control in New-Onset Hypertension and Treatment-Resistant Hypertension. *Am J Hypertens* 2018; 31: 1324-1331.
18. McGettigan P and Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med* 2013; 10: e1001388. 20130212.

19. Schmidt M, Hallas J and Friis S. Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012. *Clinical epidemiology* 2014; 6: 155-168. 2014/05/30.
20. Schmidt M and Pottegård A. Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study. *European heart journal Cardiovascular pharmacotherapy* 2020 2020/06/26.
21. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *European heart journal* 2021; 42: 3227-3337.
22. Wong CW, Kwok CS, Narain A, et al. Marital status and risk of cardiovascular diseases: a systematic review and meta-analysis. *Heart (British Cardiac Society)* 2018; 104: 1937-1948. 20180619.
23. Hu B, Li W, Wang X, Liu L, Teo K and Yusuf S. Marital status, education, and risk of acute myocardial infarction in Mainland China: the INTER-HEART study. *Journal of epidemiology* 2012; 22: 123-129. 20120114.
24. Kucharska-Newton AM, Harald K, Rosamond WD, Rose KM, Rea TD and Salomaa V. Socioeconomic indicators and the risk of acute coronary heart disease events: comparison of population-based data from the United States and Finland. *Ann Epidemiol* 2011; 21: 572-579.
25. Rosengren A, Subramanian SV, Islam S, et al. Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study. *Heart (British Cardiac Society)* 2009; 95: 2014-2022. 20091012.
26. Kilander L, Berglund L, Boberg M, Vessby B and Lithell H. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. *International journal of epidemiology* 2001; 30: 1119-1126.
27. Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML and Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: the MORGEN study. *European journal of epidemiology* 2013; 28: 807-814. 20130914.
28. Woodward M, Peters SA, Batty GD, et al. Socioeconomic status in relation to cardiovascular disease and cause-specific mortality: a comparison of Asian and Australasian populations in a pooled analysis. *BMJ open* 2015; 5: e006408. 20150317.
29. Méjean C, Droomers M, van der Schouw YT, et al. The contribution of diet and lifestyle to socioeconomic inequalities in cardiovascular morbidity and mortality. *International journal of cardiology* 2013; 168: 5190-5195. 20130729.
30. Meneton P, Kesse-Guyot E, Méjean C, et al. Unemployment is associated with high cardiovascular event rate and increased all-cause mortality in middle-aged socially privileged individuals. *International archives of occupational and environmental health* 2015; 88: 707-716. 20141111.
31. Dupre ME, George LK, Liu G and Peterson ED. The cumulative effect of unemployment on risks for acute myocardial infarction. *Archives of internal medicine* 2012; 172: 1731-1737.
32. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)* 2004; 364: 937-952.
33. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet (London, England)* 2010; 375: 2215-2222.
34. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet (London, England)* 2009; 373: 1083-1096. 20090318.
35. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B and He J. Alcohol consumption and risk of stroke: a meta-analysis. *Jama* 2003; 289: 579-588.
36. Blair SN, Kampert JB, Kohl HW, 3rd, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *Jama* 1996; 276: 205-210.

37. Gao B, Zhang L and Wang H. Clustering of Major Cardiovascular Risk Factors and the Association with Unhealthy Lifestyles in the Chinese Adult Population. *PLoS One* 2013; 8: e66780. 20130619.
38. Grundy SM, Pasternak R, Greenland P, Smith S, Jr. and Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999; 100: 1481-1492.
39. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers* 2015; 1: 15019. 20150723.
40. Stidsen JV, Henriksen JE, Olsen MH, et al. Pathophysiology-based phenotyping in type 2 diabetes: A clinical classification tool. *Diabetes Metab Res Rev* 2018; 34: e3005. 20180426.
41. Zhang YB, Chen C, Pan XF, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. *BMJ (Clinical research ed)* 2021; 373: n604. 20210414.
42. Mackenbach JP, Stirbu I, Roskam AJ, et al. Socioeconomic inequalities in health in 22 European countries. *The New England journal of medicine* 2008; 358: 2468-2481.
43. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H and Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837-1847.
44. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)* 2020; 396: 1223-1249.
45. *International Diabetes Federation. IDF Diabetes Atlas. 10th edn. Brussels, Belgium: 2021. Available at https://www.diabetesatlas.org*.
46. Gomes MB, Rathmann W, Charbonnel B, et al. Treatment of type 2 diabetes mellitus worldwide: Baseline patient characteristics in the global DISCOVER study. *Diabetes Res Clin Pract* 2019; 151: 20-32. 2019/03/25.
47. Khunti K, Chen H, Cid-Ruzafa J, et al. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: Results from the global DISCOVER study programme. *Diabetes Obes Metab* 2020; 22: 66-78. 20191001.
48. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F and Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. *BMJ Open* 2017; 7: e015949. 2017/08/02.
49. Davies LE, Kingston A, Todd A and Hanratty B. Characterising polypharmacy in the very old: Findings from the Newcastle 85+ Study. *PLoS One* 2021; 16: e0245648. 20210119.
50. Kim J, Lee J, Shin CM, Lee DH and Park BJ. Risk of gastrointestinal bleeding and cardiovascular events due to NSAIDs in the diabetic elderly population. *BMJ Open Diabetes Res Care* 2015; 3: e000133. 20151218.
51. Wami WM, Buntinx F, Bartholomeeusen S, Goderis G, Mathieu C and Aerts M. Influence of chronic comorbidity and medication on the efficacy of treatment in patients with diabetes in general practice. *Br J Gen Pract* 2013; 63: e267-273.
52. CoCites: A citation-based method for searching scientific literature, https://www.cocites.com/ (accessed 3 January 2023).
53. Bally M, Beauchamp ME, Abrahamowicz M, Nadeau L and Brophy JM. Risk of acute myocardial infarction with real-world NSAIDs depends on dose and timing of exposure. *Pharmacoepidemiology and drug safety* 2018; 27: 69-77. 20171124.
54. Masclee GMC, Straatman H, Arfè A, et al. Risk of acute myocardial infarction during use of individual NSAIDs: A nested case-control study from the SOS project. *PLoS One* 2018; 13: e0204746. 20181101.
55. Olsen AM, Fosbøl EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. *Circulation* 2012; 126: 1955-1963. 20120910.
56. Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with

prior myocardial infarction: a nationwide cohort study. *Circulation* 2011; 123: 2226-2235. 20110509.
57. Schink T, Kollhorst B, Varas Lorenzo C, et al. Risk of ischemic stroke and the use of individual non-steroidal anti-inflammatory drugs: A multi-country European database study within the SOS Project. *PLoS One* 2018; 13: e0203362. 20180919.
58. García-Poza P, de Abajo FJ, Gil MJ, Chacón A, Bryant V and García-Rodríguez LA. Risk of ischemic stroke associated with non-steroidal anti-inflammatory drugs and paracetamol: a population-based case-control study. *Journal of thrombosis and haemostasis : JTH* 2015; 13: 708-718. 20150224.
59. Ungprasert P, Matteson EL and Thongprayoon C. Nonaspirin Nonsteroidal Anti-Inflammatory Drugs and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-Analysis of Observational Studies. *Stroke* 2016; 47: 356-364. 20151215.
60. Arfè A, Scotti L, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ (Clinical research ed)* 2016; 354: i4857. 20160928.
61. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet (London, England)* 2004; 363: 1751-1756.
62. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ and Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. *BMJ (Clinical research ed)* 2011; 343: d3450. 20110704.
63. Schjerning Olsen AM, Fosbøl EL, Pallisgaard J, et al. NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction: a nationwide study. *European heart journal Cardiovascular pharmacotherapy* 2015; 1: 107-114. 20150224.
64. Schmidt M, Christiansen CF, Horváth-Puhó E, Glynn RJ, Rothman KJ and Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. *Journal of thrombosis and haemostasis : JTH* 2011; 9: 1326-1333.
65. Schmidt M, Sørensen HT and Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ (Clinical research ed)* 2018; 362: k3426. 20180904.
66. Fosbøl EL, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. *Circ Cardiovasc Qual Outcomes* 2010; 3: 395-405. 20100608.
67. Downing J, Taylor R, Mountain R, et al. Socioeconomic and health factors related to polypharmacy and medication management: analysis of a Household Health Survey in North West Coast England. *BMJ open* 2022; 12: e054584. 20220524.
68. van Oort S, Rutters F, Warlé-van Herwaarden MF, et al. Characteristics associated with polypharmacy in people with type 2 diabetes: the Dutch Diabetes Pearl cohort. *Diabet Med* 2021; 38: e14406. 20201017.
69. Silva IR, Gonçalves LG, Chor D, et al. Polypharmacy, socioeconomic indicators and number of diseases: results from ELSA-Brasil. *Rev Bras Epidemiol* 2020; 23: e200077. 20200706.
70. Kennel PJ, Kneifati-Hayek J, Bryan J, et al. Prevalence and determinants of Hyperpolypharmacy in adults with heart failure: an observational study from the National Health and Nutrition Examination Survey (NHANES). *BMC Cardiovasc Disord* 2019; 19: 76. 20190401.
71. Rawle MJ, Richards M, Davis D and Kuh D. The prevalence and determinants of polypharmacy at age 69: a British birth cohort study. *BMC Geriatr* 2018; 18: 118. 20180516.
72. Slater N, White S, Venables R and Frisher M. Factors associated with polypharmacy in primary care: a cross-sectional analysis of data from The English Longitudinal Study of Ageing (ELSA). *BMJ open* 2018; 8: e020270. 20180314.
73. Sarwar MR, Iftikhar S and Sarfraz M. Influence of Education Level of Older Patients on Polypharmacy, Potentially Inappropriate Medications Listed in Beer's Criteria, and Unplanned Hospitalization: A Cross-Sectional Study in Lahore, Pakistan. *Medicina (Kaunas)* 2018; 54 20180824.

74. Castioni J, Marques-Vidal P, Abolhassani N, Vollenweider P and Waeber G. Prevalence and determinants of polypharmacy in Switzerland: data from the CoLaus study. *BMC Health Serv Res* 2017; 17: 840. 20171221.
75. Randhawa AK, Parikh JS and Kuk JL. Trends in medication use by body mass index and age between 1988 and 2012 in the United States. *PLoS One* 2017; 12: e0184089. 20170920.
76. Husson N, Watfa G, Laurain MC, et al. Characteristics of polymedicated (≥ 4) elderly: a survey in a community-dwelling population aged 60 years and over. *J Nutr Health Aging* 2014; 18: 87-91.
77. Sigurdardottir AK, Arnadottir SA and Gunnarsdottir ED. Socioeconomic status and differences in medication use among older people according to ATC categories and urban-rural residency. *Scandinavian journal of public health* 2013; 41: 311-317. 20130213.
78. Santos TR, Lima DM, Nakatani AY, Pereira LV, Leal GS and Amaral RG. Medicine use by the elderly in Goiania, Midwestern Brazil. *Rev Saude Publica* 2013; 47: 94-103.
79. Neves SJ, Marques AP, Leal MC, Diniz Ada S, Medeiros TS and Arruda IK. Epidemiology of medication use among the elderly in an urban area of Northeastern Brazil. *Rev Saude Publica* 2013; 47: 759-767; discussion 768.
80. Pappa E, Kontodimopoulos N, Papadopoulos AA, Tountas Y and Niakas D. Prescribed-drug utilization and polypharmacy in a general population in Greece: association with sociodemographic, health needs, health-services utilization, and lifestyle factors. *Eur J Clin Pharmacol* 2011; 67: 185-192. 20101111.
81. Gokce Kutsal Y, Barak A, Atalay A, et al. Polypharmacy in the elderly: a multicenter study. *J Am Med Dir Assoc* 2009; 10: 486-490. 20090628.
82. Moen J, Antonov K, Larsson CA, et al. Factors associated with multiple medication use in different age groups. *Ann Pharmacother* 2009; 43: 1978-1985. 20091117.
83. Haider SI, Johnell K, Weitoft GR, Thorslund M and Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. *J Am Geriatr Soc* 2009; 57: 62-69. 20081114.
84. Haider SI, Johnell K, Thorslund M and Fastbom J. Analysis of the association between polypharmacy and socioeconomic position among elderly aged > or =77 years in Sweden. *Clin Ther* 2008; 30: 419-427.
85. Nielsen MW, Hansen EH and Rasmussen NK. Prescription and non-prescription medicine use in Denmark: association with socio-economic position. *Eur J Clin Pharmacol* 2003; 59: 677-684. 20031002.
86. Perry BA and Turner LW. A prediction model for polypharmacy: are older, educated women more susceptible to an adverse drug event? *J Women Aging* 2001; 13: 39-51.
87. Schmidt M and Pottegård A. Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study. *European heart journal Cardiovascular pharmacotherapy* 2021; 7: 496-506.
88. Bakhriansyah M, Souverein PC, de Boer A and Klungel OH. Risk of myocardial infarction associated with non-steroidal anti-inflammatory drugs: Impact of additional confounding control for variables collected from self-reported data. *J Clin Pharm Ther* 2019; 44: 623-631. 20190407.
89. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J and Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: the example of COX2 inhibitors and myocardial infarction. *Epidemiology* 2005; 16: 17-24.
90. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *Jama* 2015; 313: 805-814.
91. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2009; 2: 155-163. 20090505.
92. Olsen AM, Fosbøl EL, Lindhardsen J, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients--a nationwide study. *PLoS One* 2013; 8: e54309. 20130130.

93. Bavry AA, Khaliq A, Gong Y, Handberg EM, Cooper-Dehoff RM and Pepine CJ. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *Am J Med* 2011; 124: 614-620. 20110518.
94. Schmidt M, Pedersen L, Maeng M, et al. Nonsteroidal antiinflammatory drug use and cardiovascular risks after coronary stent implantation. *Pharmacotherapy* 2011; 31: 458-468.
95. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006; 113: 2906-2913. 20060619.
96. Brophy JM, Lévesque LE and Zhang B. The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction. *Heart (British Cardiac Society)* 2007; 93: 189-194. 20060718.
97. Feenstra J, Heerdink ER, Grobbee DE and Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Archives of internal medicine* 2002; 162: 265-270.
98. Hudson M, Richard H and Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ (Clinical research ed)* 2005; 330: 1370.
99. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Archives of internal medicine* 2009; 169: 141-149.
100. Barthélémy O, Limbourg T, Collet JP, et al. Impact of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular outcomes in patients with stable atherothrombosis or multiple risk factors. *International journal of cardiology* 2013; 163: 266-271. 20110629.
101. Kohli P, Steg PG, Cannon CP, et al. NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. *Am J Med* 2014; 127: 53-60.e51. 20131123.
102. Lamberts M, Lip GY, Hansen ML, et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. *Ann Intern Med* 2014; 161: 690-698.
103. Pearson-Stuttard J, Holloway S, Polya R, et al. Variations in comorbidity burden in people with type 2 diabetes over disease duration: A population-based analysis of real world evidence. *EClinicalMedicine* 2022; 52: 101584. 20220801.
104. Nowakowska M, Zghebi SS, Ashcroft DM, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. *BMC Med* 2019; 17: 145. 20190725.
105. Ohno T, Aune D and Heath AK. Adiposity and the risk of rheumatoid arthritis: a systematic review and meta-analysis of cohort studies. *Scientific Reports* 2020; 10: 16006.
106. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B and Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011; 155: 725-732.
107. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S and Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. *American journal of epidemiology* 2010; 171: 135-154. 20091211.
108. Schäfer C and Keyßer G. Lifestyle Factors and Their Influence on Rheumatoid Arthritis: A Narrative Review. *J Clin Med* 2022; 11 20221202.
109. Georgiev T and Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. *Rheumatol Int* 2019; 39: 1145-1157. 20190325.
110. Parreira P, Maher CG, Steffens D, Hancock MJ and Ferreira ML. Risk factors for low back pain and sciatica: an umbrella review. *Spine J* 2018; 18: 1715-1721. 20180521.
111. Wang X, Chan AT, Slattery ML, et al. Influence of Smoking, Body Mass Index, and Other Factors on the Preventive Effect of Nonsteroidal Anti-Inflammatory Drugs on Colorectal Cancer Risk. *Cancer Res* 2018; 78: 4790-4799. 20180619.
112. Tsujimoto T and Kajio H. No beneficial effects of aspirin on secondary cardiovascular prevention in patients with type 2 diabetes using non-steroidal anti-inflammatory drugs. *Diabetes Obes Metab* 2019; 21: 1978-1984. 20190424.

113. Tsai HJ, Hsu YH, Huang YW, Chang YK, Liu JS and Hsu CC. Use of non-steroidal anti-inflammatory drugs and risk of chronic kidney disease in people with Type 2 diabetes mellitus, a nationwide longitudinal cohort study. *Diabet Med* 2015; 32: 382-390. 20141111.
114. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clinical epidemiology* 2019; 11: 563-591. 2019/08/03.
115. Schmidt M, Pedersen L and Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *European journal of epidemiology* 2014; 29: 541-549. 2014/06/27.
116. Christensen AI, Lau CJ, Kristensen PL, et al. The Danish National Health Survey: Study design, response rate and respondent characteristics in 2010, 2013 and 2017. *Scandinavian journal of public health* 2022; 50: 180-188. 20201108.
117. Baadsgaard M and Quitzau J. Danish registers on personal income and transfer payments. *Scandinavian journal of public health* 2011; 39: 103-105. 2011/08/04.
118. Petersson F, Baadsgaard M and Thygesen LC. Danish registers on personal labour market affiliation. *Scandinavian journal of public health* 2011; 39: 95-98. 2011/08/04.
119. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L and Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical epidemiology* 2015; 7: 449-490. 2015/11/26.
120. Skjøth F, Nielsen H and Bodilsen J. Validity of Algorithm for Classification of In- and Outpatient Hospital Contacts in the Danish National Patient Registry. *Clinical epidemiology* 2022; 14: 1561-1570. 20221216.
121. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J and Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *International journal of epidemiology* 2017; 46: 798-798f.
122. Grann AF, Erichsen R, Nielsen AG, Frøslev T and Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clinical epidemiology* 2011; 3: 133-138. 20110401.
123. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L and Adelborg K. Existing Data Sources in Clinical Epidemiology: Laboratory Information System Databases in Denmark. *Clinical epidemiology* 2020; 12: 469-475. 20200518.
124. Pontet F, Magdal Petersen U, Fuentes-Arderiu X, et al. Clinical laboratory sciences data transmission: the NPU coding system. *Stud Health Technol Inform* 2009; 150: 265-269.
125. Helweg-Larsen K. The Danish Register of Causes of Death. *Scandinavian journal of public health* 2011; 39: 26-29.
126. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American journal of epidemiology* 2011; 173: 676-682. 2011/02/19.
127. Wellejus Albertsen L, Heide-Jørgensen U, Schmidt SAJ, et al. The DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI): Development, Validation and Comparison with Existing Comorbidity Indices. *Clinical epidemiology* 2020; 12: 1299-1311. 20201120.
128. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Ann Stat* 1988; 16: 1141-1154.
129. Kaplan EL and Meier P. Nonparametric Estimation from Incomplete Observations. *JASA* 1958; 53: 457-481.
130. Andersen PK, Geskus RB, de Witte T and Putter H. Competing risks in epidemiology: possibilities and pitfalls. *International journal of epidemiology* 2012; 41: 861-870. 20120109.
131. Cox DR. Regression Models and Life-Tables. *JSTOR* 1972; 34: 187-220.
132. Austin PC, Lee DS and Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016; 133: 601-609.
133. Lau B, Cole SR and Gange SJ. Competing risk regression models for epidemiologic data. *American journal of epidemiology* 2009; 170: 244-256. 20090603.
134. Walker SH and Duncan DB. Estimation of the probability of an event as a function of several independent variables. *Biometrika* 1967; 54: 167-179.

135. Armstrong BG and Sloan M. Ordinal regression models for epidemiologic data. *American journal of epidemiology* 1989; 129: 191-204.
136. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical methods in medical research* 2007; 16: 219-242. 2007/07/11.
137. Perkins NJ, Cole SR, Harel O, et al. Principled Approaches to Missing Data in Epidemiologic Studies. *American journal of epidemiology* 2018; 187: 568-575.
138. Lash TL, Vanderweele TJ, Haneuse S and Rothman KJ. *Modern Epidemiology, Chapter 14: Selection Bias and Generalizability*. 4 ed. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Wolters Kluwer, 2021, pp.315-332.
139. Hallas J and Pottegård A. Use of self-controlled designs in pharmacoepidemiology. *Journal of internal medicine* 2014; 275: 581-589. 2014/03/19.
140. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K and Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* 1990; 9: 1501-1515. 1990/12/01.
141. Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; 21: 13-15. 2009/12/17.
142. Fewell Z, Hernán MA, Wolfe F, Tilling K, Choi H and Sterne JAC. Controlling for Time-dependent Confounding using Marginal Structural Models. *The Stata Journal* 2004; 4: 402-420.
143. Xiao Y, Abrahamowicz M and Moodie EE. Accuracy of conventional and marginal structural Cox model estimators: a simulation study. *Int J Biostat* 2010; 6: Article 13. 2010/01/01.
144. Cole SR and Hernán MA. Constructing inverse probability weights for marginal structural models. *American journal of epidemiology* 2008; 168: 656-664. 2008/08/07.
145. Abel GA, Barclay ME and Payne RA. Adjusted indices of multiple deprivation to enable comparisons within and between constituent countries of the UK including an illustration using mortality rates. *BMJ open* 2016; 6: e012750. 20161115.
146. Schneeweiss S and Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *International journal of epidemiology* 2000; 29: 891-898. 2000/10/18.
147. Flanders WD and Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. *Epidemiology (Cambridge, Mass)* 1990; 1: 239-246. 1990/05/01.
148. Lash TL, Vanderweele TJ, Haneuse S and Rothman KJ. *Modern Epidemiology, Chapter 15: Precision and Study Size*. 4 ed. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Wolters Kluwer, 2021, pp.333-364.
149. Bandt CL and Boen JR. A prevalent misconception about sample size, statistical significance, and clinical importance. *J Periodontol* 1972; 43: 181-183.
150. Lakens D, Adolfi FG, Albers CJ, et al. Justify your alpha. *Nat Hum Behav* 2018; 2: 168-171.
151. Miller J and Ulrich R. The quest for an optimal alpha. *PLoS One* 2019; 14: e0208631. 20190102.
152. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014; 12: 1500-1524. 20140718.
153. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med* 2014; 29: 1060-1064. 20140123.
154. Amrhein V, Greenland S and McShane B. Scientists rise up against statistical significance. *Nature* 2019; 567: 305-307.
155. Kristensen P. Bias from nondifferential but dependent misclassification of exposure and outcome. *Epidemiology* 1992; 3: 210-215.
156. Jurek AM, Greenland S, Maldonado G and Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. *International journal of epidemiology* 2005; 34: 680-687. 2005/04/02.
157. Yland JJ, Wesselink AK, Lash TL and Fox MP. Misconceptions About the Direction of Bias From Nondifferential Misclassification. *American journal of epidemiology* 2022; 191: 1485-1495.
158. van Staa TP, Abenhaim L and Leufkens H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *Journal of clinical epidemiology* 1994; 47: 183-189.

159. Sinnott SJ, Polinski JM, Byrne S and Gagne JJ. Measuring drug exposure: concordance between defined daily dose and days' supply depended on drug class. *Journal of clinical epidemiology* 2016; 69: 107-113. 20150604.
160. Gardarsdottir H, Souverein PC, Egberts TC and Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *Journal of clinical epidemiology* 2010; 63: 422-427. 20091031.
161. Lash TL, Vanderweele TJ, Haneuse S and Rothman KJ. *Modern Epidemiology, Chapter 13: Measurement and Measurement Error*. 4 ed. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Wolters Kluwer, 2021, pp.287-314.
162. Gaster N, Hallas J, Pottegård A, Friis S and Schmidt M. The Validity of Danish Prescription Data to Measure Use of Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs and Quantification of Bias Due to Non-Prescription Drug Use. *Clinical epidemiology* 2021; 13: 569-579. 20210713.
163. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ open* 2016; 6: e012832. 2016/11/20.
164. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A and Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *Journal of clinical epidemiology* 2002; 55: 602-607. 2002/06/14.
165. Thygesen SK, Christiansen CF, Christensen S, Lash TL and Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; 11: 83. 20110528.
166. Gribsholt SB, Pedersen L, Richelsen B and Thomsen RW. Validity of ICD-10 diagnoses of overweight and obesity in Danish hospitals. *Clinical epidemiology* 2019; 11: 845-854. 20190911.
167. Chubak J, Dalmat RR, Weiss NS, Doria-Rose VP, Corley DA and Kamineni A. Informative Presence in Electronic Health Record Data: A Challenge in Implementing Study Exclusion Criteria. *Epidemiology* 2023; 34: 29-32. 20220920.
168. Ogburn EL and VanderWeele TJ. On the nondifferential misclassification of a binary confounder. *Epidemiology (Cambridge, Mass)* 2012; 23: 433-439. 2012/03/28.
169. Salas M, Hofman A and Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *American journal of epidemiology* 1999; 149: 981-983.
170. Sorriento D and Iaccarino G. Inflammation and Cardiovascular Diseases: The Most Recent Findings. *Int J Mol Sci* 2019; 20 20190809.
171. Yoshida K, Solomon DH and Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol* 2015; 11: 437-441. 20150324.
172. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016; 75: 552-559. 2015/03/04.
173. Hinz B, Cheremina O and Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *Faseb j* 2008; 22: 383-390. 20070920.
174. Henriksen DP, Rasmussen L, Hansen MR, Hallas J and Pottegård A. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. *PLoS One* 2015; 10: e0140197. 20151006.
175. Athanasiadis G, Cheng JY, Vilhjálmsson BJ, et al. Nationwide Genomic Study in Denmark Reveals Remarkable Population Homogeneity. *Genetics* 2016; 204: 711-722. 20160817.
176. Pharmaceutical / Non-steroidal Anti-inflammatory Drugs (NSAIDs) Market, https://www.fortunebusinessinsights.com/non-steroidal-anti-inflammatory-drugs-nsaids-market-102823 (accessed 6 January 2023).
177. Boye KS, Lage MJ, Shinde S, Thieu V and Bae JP. Trends in HbA1c and Body Mass Index Among Individuals with Type 2 Diabetes: Evidence from a US Database 2012-2019. *Diabetes Ther* 2021; 12: 2077-2087. 20210602.
178. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet (London, England)* 2017; 390: 2627-2642. 20171010.
179. Tomlinson G and Detsky AS. Composite end points in randomized trials: there is no free lunch. *Jama* 2010; 303: 267-268.

180. Montori VM, Permanyer-Miralda G, Ferreira-González I, et al. Validity of composite end points in clinical trials. *BMJ (Clinical research ed)* 2005; 330: 594-596.
181. Lauer MS and Topol EJ. Clinical trials--multiple treatments, multiple end points, and multiple lessons. *Jama* 2003; 289: 2575-2577.
182. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* 2020; 21 20200830.

12. Supplemental material

Supplementary Table 1. Categorization of modifiable and socioeconomic risk factors according to the questions and possible answers of the Danish National Health Survey and information on income and employment from Danish registries

Supplementary Table 2. International Classification of Diseases (ICD), Anatomical Therapeutic Chemical classification (ATC), and Nomenclature for Properties and Units (NPU) codes used in the studies

Supplementary Table 1. Categorization of modifiable and socioeconomic risk factors according to the questions and possible answers of the Danish National Health Survey and information on income and employment from Danish registries

Categories of modifiable and socioeconomic risk factors	Questions and response options
Weight status	(1) What is your weight? (2) What is your height?
	(1) Weight and (2) height stated.
Underweight	Body mass index ≤18.4.
Normal	Body mass index 18.5–24.9.
Overweight	Body mass index 25.0–29.9.
Obese	Body mass index ≥30.0.
Smoking status	Do you smoke?
Never	No, I have never smoked.
Former	No, I quit.
Current	Yes, every day; yes, at least every week; yes, less often than every week.
Alcohol consumption	How many alcoholic drinks do you consume on average each weekday?
	Numbers of beers, wine, and spirits stated.
Low-risk	Weekly alcoholic drinks ≤7 for women and ≤14 for men.
Moderate or high-risk	Weekly alcoholic drinks ≥8 for women and ≥15 for men.
Binge drinking	How often do you consume ≥5 alcoholic drinks on the same occasion?
Never or rarely	Never/Rarely.
Monthly	Monthly.
Weekly	Weekly.
Daily or almost daily	Daily/Almost Daily.
Physical activity	(2010, 2013) How would you best describe your physical activity? (2017) Hours of moderate or hard exercise per week.
High	(2010, 2013) Hard exercise and competitive sports regularly several times per week. (2017) ≥10 hours of moderate or hard exercise per week.
Moderate	(2010, 2013) Moderate exercise, heavy gardening, or similar ≥4 hours per week; walk, bicycle, or other lighter exercise ≥4 hours per week. (2017) 4–10 hours of moderate or hard exercise per week.
Low	(2010, 2013) Read, watch television, or do other sedentary involvements. (2017) <4 hours of moderate or hard exercise per week.
Marital Status	(1) What is your legal marital status? (2) What is your cohabitation status?
Never	(1) Unmarried. (2) Single (unmarried).
Former	(1) Separated, divorced, widowed. (2) Single (separated, divorced), single (widowed).
Current	(1) Married, registered partnership. (2) Married, cohabitation.
Education	(1) Have you completed a vocational education? (2) What type of education do you have?
University or higher	(1) Long higher education.
Vocational or high school	(1) Short education, short higher education, medium higher education. (2) High-school education.
Primary or other	(1) No vocational education. (2) ≤7 years of education, 8–9 years of education, 10–11 years of education.
	(1) Other education, skilled education. (2) Other (including foreign schooling).
Student	(1) Currently studying. (2) Still going to school.
None	(1) None, ≥1 shorter course.
Income*†	
Low	<$26,480
Moderate-low	$26,480–$42,862
Moderate-high	$42,862–$59,233
High	≥$59,233
Employment*	Employment.
Employed	Employment.
Unemployed	Unemployment, outside the labor force.
Pension	Pre-retirement beneficiary, early retirement beneficiary, old-age pensioner.
Other	Unemployment beneficiary, students, maternity/paternity leave, sick leave, flexible wage subsidy.

*Based on registry information

†Defined according to mean annual income in the five years before survey response

Supplementary Table 2. International Classification of Diseases (ICD), Anatomical Therapeutic Chemical classification (ATC), and Nomenclature for Properties and Units (NPU) codes used in the studies

Study cohort	**Codes**
Type 2 diabetes	ICD-10: O24, H360, G632, G590, H280, H334B, M142, N083, T383, E10–E14 ATC: A10 NPU: NPU27300, NPU03835
Exposure	**Codes**
NSAID overall	ATC: M01A
Ibuprofen	ATC: M01AE01, M02AA13
Naproxen	ATC: M01AE02, M01AE52, M01AE56, M02AA12
Diclofenac	ATC: M01AB05, M01AB55, M02AA15
Outcome	**Codes**
Myocardial infarction	ICD-10: I21 (only inpatient diagnoses)
Ischemic stroke (including transient ischemic attack)	ICD-10: G459, I63–I64
Heart failure	ICD-10: I130, I132, I420, I426–I429, I500–I503, I508–I110 (only inpatient diagnoses)
Atrial fibrillation or flutter	ICD-10: I48
Blood glucose	**Codes**
Hemoglobin A1c	NPU27300, NPU03835
Quan-modified Charlson Comorbidity Index	**Codes**
Congestive heart failure	ICD-8: 425.08, 425.09, 427.0, 427.1, 428 ICD-10: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0
Dementia	ICD-8: 290 ICD-10: F00–F03, F05.1, G30, G31.1
Chronic pulmonary disease	ICD-8: 491, 492 ICD-10: I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3 ATC: R03
Rheumatologic disease	ICD-8: 446, 696.00, 712.0–712.3, 712.5, 716, 734.0, 734.1, 734.9 ICD-10: M05, M06, M31.5, M32–M34, M35.1, M35.3, M36.0
Mild liver disease	ICD-8: 070, 571, 573 ICD-10: B18, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73, K74, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Diabetes with chronic complications	ICD-8: 250.01–250.05 ICD-10: E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Hemi or paraplegia	ICD-8: 343, 344 ICD-10: G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9
Renal disease	ICD-8: 403.99, 404.99, 582–584, 593.0, 792, Y29.01 ICD-10: I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18, N19, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Any malignancy including leukemia and lymphoma	ICD-8: 140–209 (except 173, 175–179, 208) ICD-10: C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97
Moderate or severe liver disease	ICD-8: 456.0, 571.9, 573.02, 785.3 ICD-10: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5–K76.7
Metastatic solid tumor	ICD-8: 196–199 ICD-10: C77–C80
AIDS/HIV	ICD-10: B20–B22, B24
rDANCAMI	**Codes**
Dementia	ICD-10: F00–F03, F051, G30, G311
Chronic pulmonary disease	ICD-10: I278, I279, J40–J47, J60–J67, J684, J701, J703 ATC: R03
Rheumatologic disease	ICD-10: M05, M06, M315, M32–M34, M351, M353, M360
Mild liver disease	ICD-10: B18, K700–K703, K709, K713–K715, K717, K73, K74, K760, K7.2–K764, K768, K769, Z944
Diabetes with chronic complications	ICD-10: E102–E105, E107, E112–E115, E117, E122–E125, E127, E132– E135, E137, E142–E145, E147
Hemiplegia or paraplegia	ICD-10: G041, G114, G801, G802, G81, G82, G830–G834, G839
Renal disease	ICD-10: I120, I131, N032–N037, N052– N057, N18, N19, N250, Z490– Z492, Z940, Z992
Any malignancy, including leukemia and lymphoma	ICD-10: C00–C26, C30–C34, C37– C41, C43, C45–C58, C60– C76, C81–C85, C88, C90–C97
Moderate or severe liver disease	ICD-10: I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767
Metastatic solid tumor	C77–C80
AIDS/HIV	ICD-10: B20–B22, B24

Hypertension	ICD-10: I10–I15 ATC: C02A–C02B (alfa-adrenergic blockers), C02DA, C02L, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52 (non-loop diuretics), C02DB, C02DD, C02DG, C04, C05 (vasodilators), C07 (beta-blockers), C07F, C08, C09BB, C09DB (calcium channel blockers), C09 (renin-angiotensin system inhibitors)
Diabetes without chronic complications	ICD-10: E100, E101, E109–E111, E119–E121, E129–E131, E139–E141, E149 ATC: A10A, A10B
Affective disorder	ICD-10: F30–F34, F38, F39 ATC: N06A
Drug use	**Codes**
Antiplatelets	ATC: B01AC
Anticoagulants	ATC: B01AA, B01AB, B01AE, B01AF
Angiotensin-converting enzyme inhibitors	ATC: C09A, C09B
Angiotensin receptor blockers	ATC: C09C, C09D
Beta blockers	ATC: C07
Calcium channel blockers	ATC: C07F, C08, C09BB, C09DB
Diuretics	ATC: C03, C07B–C07D, C08G, C09BA, C09DA,
Statins	ATC: C10AA
Glucocorticoids	ATC: H02AB, R03BA
Opioids	ATC: N02A
Acetaminophen	ATC: N02BE01
Anti-migraine drugs	ATC: N02C
Proton pump inhibitors	ATC: A02BC

Abbreviation: NSAID, non-steroidal anti-inflammatory drug

13. Appendix

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