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Faculty of Health Science

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Medication therapy and treatment goal achievement among persons with coronary heart disease in a general population

Guideline adherence, medication adherence and validation of medication use

Elisabeth Pedersen

A dissertation for the degree of Philosophiae Doctor – September 2021

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Summary

Aim

To assess the adherence to medication therapy for secondary prevention and achievement of treatment goals in persons with coronary heart disease (CHD) in a general population.

Methods

This project used data from the seventh wave of the Tromsø Study, alone and linked with data from the Norwegian Prescription database (NorPD). Participants self-reporting CHD were included (n = 1483). In Paper I, the associations between guideline adherence and achievement of treatment goals were assessed using logistic regression. Paper II validated the self-reported medication use by comparing by it to pharmacy dispensings from NorPD. In Paper III medication adherence was calculated based on pharmacy dispensings from NorPD, and the associations between medication adherence and blood pressure and low-density-lipoprotein (LDL)-cholesterol were explored using linear regressions.

Results

Use of lipid-lowering drugs (LLDs) was reported by 76% of the study population, antihypertensive drugs by 72% and acetylsalicylic acid (ASA) by 66%. Agreement between self-reported medication use and pharmacy dispensings was high for all three medication groups (kappa ≥0.61). Average medication adherence (proportion of days covered) was 0.94 for both LLDs and antihypertensive drugs and 0.97 for ASA. The recommended treatment goal for LDL-cholesterol was reached by 9% of the population. Achieving this treatment goal was associated with use of LLDs. Lower LDL-cholesterol was also associated with higher adherence to LLDs. The blood pressure goal was reached by 58% of the population, but achieving this goal was not significantly associated with using antihypertensive drugs. There was also no statistically significant association between adherence to antihypertensive drugs and lower systolic or diastolic blood pressure.

Conclusions

Use of and adherence to medications for secondary prevention of CHD was high, but achievement of treatment goals for blood pressure and especially LDL-cholesterol was low. Our results indicate that the lipid-lowering and antihypertensive therapy is not sufficiently intense. The prescription level might be a potential target to improve achievement of treatment goals among persons with CHD and hence prevent new CHD events.

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Abbreviations

ACE	angiotensin converting enzyme
ADP	adenosine-diphosphate
AP	angina pectoris
ARB	angiotensin receptor blocker
ASA	acetylsalicylic acid
ATC	anatomical therapeutic chemical
BMI	body mass index
CABG	coronary artery bypass grafting surgery
CCB	calcium channel blocker
CHD	coronary heart disease
CI	confidence interval
CMA	continuous multiple-interval measure of medication availability
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DDD	defined daily dose
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EUROASPIRE	EUROpean Action on Secondary Prevention through Intervention to Reduce Events
GP	general practitioner
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
JES	Joint European Societies
LDL	low-density-lipoprotein
LLD	lipid-lowering drug
MI	myocardial infarction
MICE	multiple imputation by chained equations
MPR	medication possession ratio
NorPD	Norwegian Prescription Database
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PCI	percutaneous coronary intervention
PDC	proportion of days covered
PPV	positive predictive value
SMD	standardized mean difference
WHO	World Health Organization

List of papers

Paper I:

Pedersen E, Garcia BH, Halvorsen KH, Eggen AE, Schirmer H, Waaseth M. Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7. BMC cardiovascular disorders. 2021;21(1):44.

Paper II:

Pedersen E, Truong KNL, Garcia BH, Halvorsen KH, Svendsen K, Eggen AE, Waaseth M. Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data. Journal of clinical epidemiology. 2021;135:115-24.

Paper III:

Pedersen E, Primicerio R, Halvorsen KH, Eggen AE, Garcia BH, Schirmer H, Waaseth M. Medication adherence among persons with coronary heart disease and associations with blood pressure and low-density-lipoprotein-cholesterol. Manuscript submitted for publication.

1 Introduction

1.1 This thesis

This thesis investigates the use of medications for secondary prevention of coronary heart disease (CHD) and achievement of treatment goals for blood pressure and low-density-lipoprotein (LDL)-cholesterol in a general population with CHD. The project consists of three papers using data from the seventh wave of the Tromsø Study (Tromsø 7) linked with data from the Norwegian Prescription Database (NorPD) and included participants with self-reported CHD. In the first paper we described the use of antihypertensive drugs, lipid-lowering drugs (LLDs) and acetylsalicylic acid (ASA) among these participants and their achievement of treatment goals for blood pressure and LDL-cholesterol. We also assessed the association between use of antihypertensive drugs and achievement of the treatment goal for blood pressure as well as between use of LLDs and achieving the treatment goal for LDL-cholesterol. In the second paper we validated the self-reported use of antihypertensive drugs, LLDs and ASA by comparing the self-reported information with dispensing data from NorPD and explored different methods of defining current medication use in NorPD. In the third paper, we calculated proportion of days covered (PDC) as a measure of medication adherence to antihypertensive drugs, LLDs and ASA based on dispensing data from NorPD and assessed the association between adherence to antihypertensive drugs and systolic and diastolic blood pressure, and between adherence to LLDs and LDL-cholesterol levels.

1.2 Coronary heart disease

CHD, also called coronary artery disease or ischemic heart disease, is a major cause of death worldwide (1). In developed countries, the age-standardized CHD mortality rate has decreased over the last decades and is now surpassed by cancer as the most common cause of death in several countries, including Norway (2). Reduced mortality is a result of better CHD prevention and improved acute treatment (3, 4). As more patients survive acute CHD events, the prevalence of persons living with CHD rises. Having suffered a CHD event increases the risk of experiencing a new event (5), and as the number of persons surviving CHD events increases, optimal secondary prevention treatment is becoming increasingly important in a public health perspective.

1.2.1 Disease mechanism, revascularization procedures and risk factors of CHD

CHD occurs as a result of reduced oxygen supply to the heart (6). This is usually caused by a blockage of the coronary arteries, thus preventing blood from flowing to the heart. The most common cause of the blockage is build-ups of cholesterol-rich fatty deposits on the inner walls of the coronary arteries (6, 7). A partial blockage of the arteries leads to angina pectoris (AP), while a complete blockage or severely reduced blood flow results in a myocardial infarction (MI) (8).

A method used to open the blocked coronary arteries is percutaneous coronary intervention (PCI). The procedure involves leading a guide catheter through the arteries from the wrist or groin to the coronary arteries (9). Then a thin guidewire with a deflated balloon is led in through the catheter to the blockage. At the blockage the balloon is inflated to press the plaque blocking the artery towards the artery walls thus widening the coronary artery's diameter and restoring the blood flow to the heart. The balloon is then deflated and removed. In the PCI process, it is common to insert a stent in the blocked area of the coronary artery to ensure that the artery stays open. The stent can either be bare metal or drug-eluting. Drug-eluting stents contain medications that inhibit growth of new tissue in the area around the stent, thereby preventing new blockage of the stented artery, known as restenosis (9, 10).

In some cases coronary artery bypass graft surgery (CABG) is preferred over PCI as a method of restoring blood flow to the heart (10). This surgery is conducted by moving blood vessels from the chest cavity, thighs or legs and connect them between the coronary arteries and the aorta, bypassing the blocked area (11).

Persons with CHD have increased risk of new cardiovascular events and death. Secondary prevention is therefore important to lower this risk. The major modifiable risk factors for CHD include hyperlipidemia, hypertension, smoking, unhealthy diet, diabetes and low physical activity (6, 12, 13). Secondary prevention of CHD targets these risk factors, both through lifestyle changes and pharmacological treatment. Lifestyle modifications, including smoking cessation, increased physical activity and adopting a healthier diet are highly recommended. However, as this is not enough to lower the risk sufficiently, guidelines also

stress the importance of using medications to lower cholesterol and blood pressure, and antiplatelet drugs to prevent blood clotting (12, 13).

1.2.2 Medications used for secondary prevention of CHD

The most common medications used for secondary prevention of CHD are described below.

Lipid-lowering drugs (LLDs)

Statins

The most prescribed LLDs worldwide are statins. These are also specifically recommended as the first choice of lipid-lowering treatment by clinical practice guidelines in Europe (14). Statins are recommended to all patients with CHD. There are six different statins authorized for sale in Norway; atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin, whereof simvastatin and atorvastatin are the most used (15).

Statins' mode of action is through inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase and they are therefore also known as HMG-CoA reductase inhibitors (16). HMG-CoA reductase is important for formation of precursors of several biological substances, including cholesterol. Reduced cholesterol formation leads to an increase in LDL-receptors in the liver and hence increased uptake of LDL-cholesterol from the blood and increased metabolism in the liver. This reduces blood concentrations of total cholesterol, LDL-cholesterol, triglycerides and apolipoprotein B, and increases concentrations of high-density lipoprotein (HDL)-cholesterol (16).

Other LLDs

If statins are not tolerated or insufficient to lower lipids to the recommended level, substitution with or addition of other LLDs such as ezetimibe is possible. Other substances such as cholesteryl ester transfer protein inhibitors, bile acid sequestrants and nicotinic acid can also contribute to reduction of lipids but are not commonly used (16).

Ezetimibe binds to a protein that transports cholesterol from the intestine, thus inhibiting absorption of cholesterol (14). This leads to increased expression of LDL-receptors in the liver, hence increasing the cholesterol-lowering effect. A combination of ezetimibe and a statin leads to stronger lipid-reduction than when used separately (17).

In the last decade a new class of LLD has been developed, known as proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors (18). PCSK9 is an enzyme that binds to the liver's LDL-receptors and leads to their degradation (16). Fewer LDL-receptors results in less LDL-cholesterol being absorbed into the liver and hence higher concentrations in the blood. PCSK9-inhibitors bind to PCSK9 and thereby prevent the degradation of the LDL-receptor and thus more LDL-cholesterol is being removed from the blood (18). Though PCSK9-inhibitors are found to be highly effective, their use is limited due to their high costs (19).

Antihypertensive drugs

Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin receptor blockers (ARBs)

ACE-inhibitors and ARBs are among the most used antihypertensive drugs in Norway as well as the rest of the world (15, 20). They are especially recommended for those with a combination of hypertension and diabetes because of their advantageous effects against nephropathy, as well as for patients with reduced left ventricular function (20, 21).

Both ACE-inhibitors and ARBs exhibit their main effect by inhibiting the activity of angiotensin II, ACE-inhibitors by inhibiting the enzyme ACE which converts angiotensin I to angiotensin II, and ARBs by blocking the angiotensin II type 1 receptor (21). Angiotensin II is a potent vasoconstrictor peptide, hence its inhibition leads to vasodilatation and reduction in total peripheral resistance. Release of aldosterone is also dependent of angiotensin II, and by reducing aldosterone release, more blood flows through the kidneys and more sodium and water is excreted (22). Lower blood volume reduces blood pressure.

Beta-blockers

Beta-blockers have for a long time been recommended as a part of the standard treatment of secondary prevention of CHD. Their effect on reducing risk of sudden death or reinfarction has been thoroughly documented. However, the studies documenting this effect are from a time before optimalization of revascularization procedures which were described in section 1.2.1 (23, 24). It is now therefore debatable whether beta-blockers should be recommended to all patients after an MI, or if the recommendation only should include the patients at highest risk, where the effect is shown to be strongest (24, 25). Currently, there are ongoing studies examining beta-blockers' role in secondary prevention of CHD, including one study from Norway (26).

Irrespective of whether beta-blockers should be routinely used for secondary prevention of CHD, it does have a role in antihypertensive treatment. Beta-blockers bind reversibly to beta-adrenergic receptors (21). This leads to many different effects in many different sites in the body. For blood pressure reduction, several mechanisms are involved, leading to reduction in cardiac output, vasodilatation, decreased heart rate and a reduction in the hearts contractility and need of oxygen (21).

Calcium-channel blockers (CCBs)

CCBs inhibit movement of calcium ions through calcium channels in vascular smooth muscle and the heart (21). Their effect on the vascular smooth muscle leads to vasodilation, while the CCBs with direct effects on the heart contribute to reduced heart rate and contraction. Dihydropyridines, which are the most used CCBs for hypertension, mainly affect vascular smooth muscles, while the CCBs with more specific effect on heart rate and contractility are mainly used for other indications than hypertension (21).

Thiazides

Thiazides bind to the distal tubular sodium/chloride cotransporter in nephrons, thus inhibiting reabsorption of sodium and chloride and resulting in their excretion (21). This also increases excretion of water, which lowers the volume of blood plasma and in that way reduces blood pressure. Thiazides also have an additional vasodilating function, which contributes to reduced blood pressure.

Other antihypertensive drugs

In addition to the antihypertensive drug classes mentioned above, other medications with antihypertensive effects exist but are not as much used, at least not for the indication of hypertension (20). However, if combining the above-mentioned drug classes does not give the required antihypertensive effect, addition of a potassium-sparing diuretic, also known as an aldosterone antagonist or mineralocorticoid receptor antagonist, is usually the next step (20). These work by binding to mineralocorticoid receptors and thereby inhibit binding of aldosterone (21). Reduction of blood pressure is thus caused by reduced reabsorption of sodium in the distal tubule in the nephron, and thereby increased excretion of sodium and water.

Antiplatelet drugs

Acetylsalicylic acid (ASA)

European guidelines for secondary prevention of CHD recommend ASA as the first-line choice of antiplatelet drug (12, 13). ASA has been shown to effectively reduce serious cardiovascular events and death, but due to its potential of increasing the risk of major bleeding, it is only recommended as secondary, and not primary, prevention (27). In low doses ASA binds irreversibly to the enzyme cyclooxygenase-1 (COX-1) in blood platelets, and hence inhibits the formation of thromboxane A_2 which again reduces the platelets' ability to aggregate (28).

Other antiplatelet drugs

If ASA is not tolerated, adenosine-diphosphate (ADP) receptor antagonists, especially clopidogrel, can be alternatives. ADP-receptor antagonists inhibit the purinergic receptor $P2Y_{12}$ (28). Inhibition of $P2Y_{12}$ deactivates glycoprotein IIb/IIIa which again leads to decreased thromboxane formation and hence reduced platelet aggregation.

The first 12 months after MI or PCI, dual antiplatelet therapy (DAPT) is recommended (12, 13, 29). This consists of ASA combined with an ADP-receptor antagonist, usually clopidogrel. DAPT has documented effect on prevention of new coronary events and death, but also increases the risk of major bleeding. As the risk of major bleeding is proportionally related to its duration of use, the ADP-receptor antagonist is recommended to be discontinued after 12 months, while treatment with ASA continues indefinitely. The optimal duration of DAPT is however still to be determined (29).

1.2.3 Treatment goals in European guidelines

The Joint European Societies (JES) have published guidelines on secondary prevention of CHD throughout the last twenty-seven years. The first Joint Task Force, consisting of the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS) and the European Society of Hypertension (ESH), published the first guideline in 1994 (30). The sixth, and most recent, guideline from the JES was published in 2016 (13). All editions of the guidelines have focused on the treatment of modifiable risk factors for CHD: cholesterol, blood pressure, diabetes control, smoking, body weight and physical activity.

The most recent guidelines from 2016 (13) recommend that all persons with CHD stop smoking if they are smokers, reduce body weight if overweight or obese, preferably to normal

body weight (BMI of 20-25 kg/m^2), and attain moderate aerobic physical activity at least 150 minutes or vigorous physical activity at least 75 minutes a week. In persons with CHD who also have diabetes, glycated hemoglobin (HbA1c) <7.0% (<53 mmol/mol) should be aimed for. As this project focused on blood pressure and cholesterol, treatment goals for these are described in more detail below.

Blood pressure

As hypertension is a major risk factor of recurrent CHD events, as well as other conditions such as heart failure, stroke, atrial fibrillation and renal failure, blood pressure control is very important in high-risk patients. The recommended treatment goal for persons with CHD has generally been stable since the JES guidelines from 1994 (see Table 1). All the six guidelines recommend a blood pressure of <140/90 mmHg, except for the one from the Fourth Joint Task Force from 2007. In these guidelines the recommendations for persons with established CVD was a blood pressure of <130/80 mmHg if feasible (31).

The risk of death from cardiovascular diseases is found to increase from systolic blood pressure levels of 115 mmHg and diastolic blood pressure levels of 75 mmHg and upwards (32). The results of the Systolic Blood Pressure Intervention Trial (SPRINT) from 2015 found that reducing systolic blood pressure to <120 mmHg showed reduced rates of the combined outcome of death from any cause and fatal and non-fatal major cardiovascular events compared to a systolic blood pressure goal of <140 mmHg (33). More serious adverse effects were however found in the intervention group. The participants and study personnel were not blinded to study-group assignment and this may have affected the results. Evidence from reliable randomized controlled trials concerning the optimal treatment target for blood pressure among persons with CHD is scarce. The guidelines agree that there is sufficient evidence to recommend lowering blood pressure to below 140/90 mmHg but request more research before deciding to recommend even lower blood pressure targets (12, 13).

Effects of blood pressure reduction are in some studies found to be greater in patients with diabetes than in the general population. The treatment goal for blood pressure could therefore differ from that for the general CHD population. However, also in diabetes patients there is little evidence from randomized controlled studies on which to base the recommendations. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial

compared intensive blood pressure lowering treatment that targeted a systolic blood pressure <120 mmHg and standard therapy targeting a systolic blood pressure of <140 mmHg. The trial did not find any significant difference in the rate of the composite outcome of major cardiovascular events (34). Increased rate of adverse effects was seen in the intensive treatment group.

Though risk of adverse effects in the elderly is a concern, there is now evidence that blood pressure lowering treatment in elderly hypertensive persons, including those >80 years of age, is as beneficial as treatment in younger patients (35). However, as the frailest elderly persons are not usually included in studies, it is unknown whether these results are generalizable to them. In the 2016 guidelines on cardiovascular disease prevention it is therefore recommended to lower systolic blood pressure to 140-150 mmHg in elderly >60 years of age who have a systolic blood pressure ≥160 mmHg, so long as this is tolerated by the individual patient (13).

Cholesterol

As atherosclerosis is known to cause CHD, lipid control is very important in secondary prevention of CHD. The JES guidelines from 1994 started with a recommendation of reducing total cholesterol to <5.5 mmol/L (30) (see Table 1). In the next guideline from 1998, this was reduced to <5.0 and a separate treatment goal for LDL-cholesterol was introduced at <3.0 mmol/L (36). The most recent guidelines from 2012 and 2016 focus mainly on LDL-cholesterol and recommend LDL-cholesterol levels based on total cardiovascular risk. Persons with moderate risk are recommended an LDL-cholesterol of <3 mmol/L, those with high risk an LDL-cholesterol of <2.5 mmol/L or a reduction of at least 50% from baseline. Those at very high risk, which includes all with established CHD, are recommended an LDL-cholesterol of <1.8 mmol/L or a reduction of at least 50% from baseline (12, 13). In newer guidelines from ESC, including the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes and the 2019 ESC/EAS Guidelines for the management of dyslipidemias, the treatment goal for LDL-cholesterol is reduced even further to <1.4 mmol/L and at least 50% reduction from baseline (14, 37). There is even a suggestion of reducing LDL-cholesterol to <1.0 mmol/L in those who have experienced two cardiovascular events in two years (37). Though the treatment goal has continuously been lowered, reaching these treatment goals in persons with CHD remains a challenge.

Table 1: Treatment goals in guidelines from the Joint European Societies

Guideline	**Year**	**Total cholesterol CHD, mmol/L**	**LDL-cholesterol CHD, mmol/L**	**Blood pressure CHD, mmHg**	**Blood pressure CHD+ Diabetes, mmHg**
Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension (30)	1994	<5.5	-	<140/90	<140/90
Prevention of coronary heart disease in clinical practice: Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention (36)	1998	<5.0	<3.0	<140/90	<140/90
European guidelines on cardiovascular disease prevention in clinical practice Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts) (38)	2003	<4.5	<2.5	<140/90	<130/80
European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts) (31)	2007	<4.5	<2.5	<130/80	<130/80
European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) (12)	2012	-	<1.8	<140/90	<140/80
2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) (13)	2016	-	<1.8	<140/90	<140/85

1.2.4 Adherence to prescription guidelines and achievement of treatment goals

The EUROpean Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) surveys have assessed lifestyle, risk factors and use of medications for secondary prevention of CHD in Europe. The results from the first survey were published in 1997 and explored medication use and achievement of treatment goals based on the first JES guideline from 1994 (39). Since then, four more surveys have been conducted: EUROASPIRE II (40), III (41), IV (42) and V (43). Comparisons of the EUROASPIRE surveys have found that the proportion of CHD patients using medications for secondary prevention has increased, as well as the proportion having total cholesterol, LDL-cholesterol and blood pressure control (44-46). However, there is still a large proportion of CHD patients that do not reach the recommended treatment goals, especially the treatment goal for LDL-cholesterol. The most recent survey, EUROASPIRE V, conducted in 2016-2017, found that although 93% used antiplatelet drugs, 95% antihypertensive drugs and 84% LLDs, only 58% had a blood pressure <140/90 mmHg (<140/85 if diabetic) and 29% had an LDL-cholesterol of <1.8 mmol/L (43).

Though the number of countries being included in the EUROASPIRE surveys has increased from nine in EUROASPIRE I to twenty-seven in EUROASPIRE V, Norway has not been included in any of the surveys. Prescription of secondary preventive medications after acute myocardial infarction in Norway in 2009-2013 has been described by Halvorsen et al (47). They found that 91% of the patients were discharged with a prescription of antiplatelet drugs, 90% with a prescription of statins, 82% with beta-blockers and 60% with ACE-inhibitors or ARBs. After 12 months 84% of the patients were still being dispensed ASA and statins, while 77% and 57% were being dispensed beta-blocker and ACE-inhibitors or ARBs respectively (47).

Secondary prevention of CHD and achievement of treatment goals have also been investigated in Norway through the NOR-COR study (48). The NOR-COR study was conducted at the two Norwegian hospitals in Drammen and Vestfold in the southeast of Norway and included 1127 patients discharged from the hospitals in 2011-2014 after an acute MI, CABG or PCI. At follow-up 2-36 months after discharge 93% were found to use antihypertensive drugs and statins, while 97% used at least one antiplatelet drug. Despite the

high use of secondary preventive medications, 46% had a blood pressure of ≥140/90 mmHg (140/80 mmHg if diabetic) and 57% had an LDL-cholesterol concentration of ≥1.8 mmol/L at follow-up (49). The results from both EUROASPIRE and NOR-COR show that though medication use for secondary prevention after a CHD event is high, achievement of the treatment goals for blood pressure and LDL-cholesterol are far from optimal.

1.3 Measuring medication use

To assess adherence to prescription guidelines, medication use needs to be determined. Several methods exist for determining use of medications for secondary prevention of CHD. The most frequently used methods include self-report and assessment of prescribed medications based on either medical or pharmacy records (50-53).

1.3.1 Self-report

Self-reported medication use is usually collected either by questionnaires or interviews (51, 52), and in some cases medication inventories (54). For medication inventories participants are asked to bring along the medications they use or show them to the investigator when being interviewed at home.

Self-administered questionnaires are common tools for measuring medication use. They are structured instruments that allow collection of information from a large number of persons (52). There are some limitations to using questionnaires. To collect information about medication use, the persons answering the questionnaires are required to state and remember all of their medications. Some respondents may have problems remembering or may be unwilling to report all the medications they use, and others may even report medications they know they ought to be using but do not use (55).

Interviews are also applied as a way of measuring medication use. They can have a strict structure similar to self-administered questionnaires or be in more flexible forms. During less rigid interviews additional information can be obtained and questions can be adjusted individually to each of the respondents (51). They also allow for more clarification of the questions and result in higher completeness than structured questionnaires (52). Despite of its advantages, interviews are more time consuming and resource demanding than questionnaires

(52), and also affected by the same problems concerning recall and potential unwillingness to report actual medication use (55).

1.3.2 Prescriptions

In contrast to self-reported medication use, information about prescriptions is collected objectively and non-differentially. This can be done by examining medical records or assessing prescription databases, covering prescribed and/or dispensed medications (50, 52, 53).

Examining medical records to define if medications are prescribed and used according to guidelines is not uncommon. Though it does give a clear indication of which medications have been prescribed to the patients, it does not account for primary non-adherence (53). The same is true for databases only including information about prescriptions and not dispensings.

Prescriptions that have been dispensed are more likely to be used (53). Databases containing information about dispensed medications are therefore more reliable sources when defining medication use. However, many such databases are incomplete, as they are based on claims from selected insurance companies or pharmacies (56). Other potential limitations arise when the medications examined are available over-the-counter (OTC) or as free samples distributed by health care professionals (53).

Scandinavian national prescription databases do not have these limitations, as they are complete databases including all dispensed medications from all national pharmacies to all ambulatory individuals irrespective of reimbursement (57). Another advantage is that these registries can be linked to other databases, health surveys and other clinical studies using the unique national identity number assigned to all citizens.

Even when using complete prescription databases, defining which medications are in use at a certain timepoint is a challenge. The two most common methods of defining medication use at a certain date are fixed-time window, also called fixed look-back period, and the legend-time method, also known as legend-duration or medication-on-hand (58, 59). While fixed-time window defines a medication in use as having a prescription dispensed within a defined time period before the date of interest, legend-time method uses the amount dispensed to calculate whether this should be enough to last to this date. These two methods work best for

medications used daily with regular dosages. For medications with varying use or dosages, more complex methods like for instance reverse waiting time distribution (60) might be needed.

Another limitation of using dispensing data to define medication use is that it is not possible to confirm that the dispensed medication is actually taken or whether it is taken but not as indicated by the prescriber (53).

1.3.3 Validity

As all the measurement methods have limitations, none of them can provide information about the true medication use. To consider the validity of the different methods of examining medication use, studies have compared the different data sources. Since there is no absolute gold standard for measuring medication use, some studies have only looked at agreement between self-report and dispensing data (61-69), while others have also assessed validity using either self-report, dispensing data or both as reference standards (58, 70-81).

When investigating medications used on a chronic basis, agreement between self-report and pharmacy dispensing data is generally found to be high (68). For medications used as needed, agreement tends to be lower. Cardiovascular drugs are used on a daily basis, and self-reported use of these medications is generally found to have high agreement with prescription or dispensing data (65, 66, 68).

Most studies comparing self-reported and dispensed LLDs find substantial to almost perfect agreement with kappa-values of 0.67-0.95 (61, 62, 69, 71-75). Studies assessing validity using dispensing data as the reference source find high validity of self-reported LLDs with sensitivities of 87-97% and specificities of 88-99% (70, 73-75).

Agreement between self-reported use and dispensing data concerning antihypertensive drugs as a group is mostly found to be substantial with kappa-values of 0.61-0.71 (63, 72, 74). However, one study finds only moderate agreement (77), while others find agreement to be almost perfect (71, 73). Sensitivity of self-reported antihypertensive use is generally found to be at least 86% and in one study even as high as 99% (73, 74, 76, 78).

Low-dose ASA is available OTC in most countries, which makes validating self-reported use difficult. Lower agreement and validity than for LLDs and antihypertensive drugs would therefore be expected. Despite this, most studies having investigated agreement and validity of self-reported ASA generally find at least substantial agreement with dispensing data (63, 73, 79).

Although self-reported use of LLDs, antihypertensive drugs and antiplatelet drugs is mostly found to have substantial agreement with dispensing data or quite high validity, the results vary. Studies have included diverse populations and assess medication use by different methods. In addition, none of the studies have investigated medication use solely for secondary prevention of CHD.

1.4 Medication adherence

In addition to establish which medications that are used, adherence to these medications is an important factor to achieve the best possible CHD preventive effect. The World Health Organization (WHO) defines adherence as "The extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (82).

Other terms have sometimes been used interchangeably with adherence, namely compliance and concordance (83). There are however subtle differences between the terms, particularly regarding the relationship between the patient and the health care provider. Compliance is often defined as "the extent to which the patient's behavior matches the prescriber's recommendations" (83), and thereby describes the relationship between the health care provider and the patient as hierarchical, where the prescriber decides on the treatment and the patient is expected to follow it without question. Concordance, on the other hand, focuses on the process of reaching a consensus about the treatment between the patient and health care provider and was originally defined as "a new approach to the prescribing and taking of medicines. It is an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken. Although reciprocal, this is an alliance in which the health care professionals recognize the primacy of the patient's decisions about taking the recommended medications" (83). A study assessing the terms used in publications from 1961

to 2009 found that nearly all publications used the term compliance from mid-1970, before adherence became increasingly used from mid-1980s and was the most used term from the mid-2000s (84). Concordance was used occasionally from the late the 1990s, with a top about 2006-2008 before declining again in 2009.

To simplify the comparison between studies exploring adherence, a taxonomy for adherence was described in 2012 (84). This taxonomy divides the adherence process into three phases: initiation, implementation and discontinuation. Initiation signifies the start of the treatment and can either be measured as a binary measure, starts treatment or not, or as time from prescription to initiation. Implementation is the extent to which a person actually follows the prescribed dosing regimen from initiation to discontinuation. Discontinuation marks the end of treatment, hence the last dose taken after which no more doses are registered. Persistence is the time measured from initiation until discontinuation (84).

There is no optimal way of measuring adherence as this would require a feasible method of ascertaining whether the prescribed dosage regimen is indeed followed by the patient, including if, when and how the doses are ingested. The most reliable method of assessing adherence is directly observed therapy (85), but this method is generally not practical in most settings. Other direct approaches to adherence measurement include therapeutic drug monitoring and the use of ingestible sensors or addition of biological markers to the medication formulations (85-87). Indirect measurement methods are more widely utilized. The most common ways of measuring adherence are through pharmacy dispensing records or self-report, either in form of interviews, diaries or questionnaires. Other indirect methods include pill counts, measuring clinical responses or using electronic drug monitors (85, 86).

Pharmacy dispensing records can be used to calculate a range of adherence and persistence measures, including measures of medication availability, discontinuation/continuation, switching, medication gaps and refill compliance (88). Measures that assess medication availability are most applied, and of these measures medication possession ratio (MPR) and proportion of days covered (PDC) are the most common approaches (89). These methods are similar, and the names are sometimes used interchangeably, though there are subtle differences between them. The most commonly used cut-off to define participants as being adherent or as having high adherence is an MPR or PDC $\geq$0.80 (90). This cut-off is

considered arbitrary and is often used to be able to compare results between studies. There has been some research finding that for medications used for cardiovascular disease (CVD), those with a PDC ≥0.80 have a lower risk of hospitalizations and cardiovascular events than those with a PDC <0.80 and therefore this cut-off could be considered reasonable for these medications (91, 92). However, another study insist that the cut-off depends on which medication is studied and that the optimal cut-off varies between medications, also those in the same groups such as statins (93).

1.4.1 Adherence to medications used for CHD and associations with clinical outcomes

Comparing results from studies examining adherence to medications used for CHD is complicated by use of different methods of measuring and calculating adherence. All studies do however agree that adherence to medications used for secondary prevention is suboptimal and hence has potential for improvement. A systematic review from 2015 found that medication adherence for secondary prevention of CHD within one year of hospital discharge ranged from 54% to 86% (94), while a meta-analysis from 2012 found a summery estimate of adherence of 66% for those using cardiovascular drugs for secondary prevention (95).

Non-adherence to medications used for prevention of CHD has been found to increase the risk of cardiovascular death and other major cardiovascular events (96-99). Increased healthcare costs are also found among those who are non-adherent compared to those defined as adherent (97).

1.4.2 Barriers to adherence for medications used for CHD and interventions to overcome them

The WHO has classified barriers to optimal medication adherence into five categories: patient-related factors, health system/health care team-related factors, condition-related factors, therapy-related factors and socioeconomic-related factors (82). Examples of patient-level factors are forgetting to take medications, intentionally avoiding taking medications e.g. because of side-effects, low health literacy and health beliefs and attitudes (86, 100, 101). Factors related to the health care system or health care team include problems obtaining the medications, e.g. because the drug is unavailable (drug shortage), or that the medication is unaffordable for the patients (86, 100). Condition-related factors include severity of the

disease and level of disability, while therapy-related barrier could be prescription of complex medication regimes, e.g. high dosing frequency or polypharmacy (82, 101). Socioeconomic factors have not consistently been found to affect adherence, but factors that could influence medication adherence include education, income and literacy (82, 101).

Most interventions aiming to increase adherence to medications used for CHD have targeted patient-level barriers and have included patient education or counselling, reminders or medication aids and providing psychosocial support (102, 103). A meta-analysis including sixteen studies examining interventions to improve adherence to multiple cardiovascular medications in CHD patients found that the interventions significantly improved medication adherence in their pooled results, and that there were no significant differences between intervention types (102).

Adherence interventions do however not necessarily lead to lower blood pressure and LDL-cholesterol. Even in studies finding significantly improved adherence to antihypertensive drugs or LLDs in the intervention group compared to the control group, blood pressure and LDL-cholesterol control is often not significantly improved (104-108).

1.5 Summary

CHD is one of the leading causes of morbidity and mortality worldwide. As more patients survive acute CHD events, optimal secondary prevention is increasingly important for a growing chronic CHD population and thus for public health. Despite this, risk factor control, including blood pressure and LDL-cholesterol levels, in this patient group remains suboptimal. The proportion of users of medications for secondary prevention, including antihypertensive drugs, LLDs and ASA, during the first years after the CHD event has increased and is now generally found to be high. Guideline adherence and achievement of treatment goals for blood pressure and LDL-cholesterol have however not been thoroughly explored in general populations with chronic CHD, as opposed to in the first few years after the CHD event (43, 49), and the association between use of, and adherence to, these medications and achievement of treatment goals needs further investigation.

2 Aims

The overall aim of the thesis was to assess the adherence to medication therapy for secondary prevention and achievement of treatment goals in persons with CHD in a general population.

The specific objectives were:

Paper I

Describe and compare adherence to prescription guidelines for persons with CHD and explore its association with treatment goal achievement for blood pressure and LDL-cholesterol.

Paper II

Validate self-reported use of medications for secondary prevention of CHD by comparing self-report with pharmacy dispensing data and explore different methods for defining medication use in a prescription database.

Paper III

Describe adherence to medications used for secondary prevention of CHD and explore its association with LDL-cholesterol, systolic and diastolic blood pressure.

3 Methods

3.1 Data sources

3.1.1 The Tromsø Study

The Tromsø Study is an epidemiological population-based health study that has been conducted seven times between 1974 and 2016. The study population consists of inhabitants in the municipality of Tromsø, Norway, a town with approximately 73,000 inhabitants in 2016.

This project used data from the seventh wave of the Tromsø Study (Tromsø 7). Tromsø 7 was conducted in 2015-2016 and invited all inhabitants in the municipality ≥ 40 years (n = 32,591) to participate. The response rate was 65% (n = 21,083).

The participants of Tromsø 7 received an invitation and a questionnaire (Q1) in paper-format by mail. The invitation included a username and password for Q1 for those who preferred to fill it in digitally. Links to a second questionnaire (Q2) and a graphical index of pain questionnaire were also included in the invitation, and these were only available electronically. Participants could fill in the questionnaires at home or the examination site where they could get assistance if needed. The invitation to Tromsø 7 is included in Appendix 1 (Norwegian only). English translations of the questionnaires are available at the Tromsø Study's webpage (109) and the pages relevant for this project are included in Appendix 2 and 3.

At attendance all the participants went through a health examination, consisting of anthropometric measurements (height, weight, waist and hip circumference), and measurement of blood pressure, heart rate and oxygen saturation. Blood samples for analysis of blood lipids, HbA1c, creatinine and more were also taken.

3.1.2 The Norwegian Prescription Database (NorPD)

The NorPD contains information about all prescriptions dispensed at Norwegian pharmacies since 1st of January 2004, irrespective of reimbursement (110). All pharmacies in Norway are obliged to submit electronic information about all dispensed prescriptions to persons in

ambulatory care. Deliveries of medications to nursing homes and other medical institutions are also registered in NorPD, but not on an individual level. OTC medications are not included in the database, unless dispensed by prescription.

Prescription records stored in the database includes information about the prescriber, the patient for whom the medication was prescribed, the pharmacy where the prescription was dispensed, and the medications dispensed. About the prescriber, NorPD contains information about gender, month and year of birth, profession and specialty, while information about the patient include gender, month and year of birth, potential month and year of death as well as place of residence. Name, license number, municipality and county are registered about the pharmacy. Information about the medications dispensed include brand names, strength, package sizes, number of packages, anatomical therapeutic chemical (ATC) codes, number of defined daily doses (DDDs), codes of reimbursement, dispensing dates and prices (110). Areas of application and prescribed dose are also registered in the database, however, these are in free-text and not yet available for research.

3.2 Study design

This project was a cross-sectional study with a retrospective component. Paper I was a pure cross-sectional study. Paper II and Paper III included a retrospective component by including prescriptions dispensed before attendance in Tromsø 7.

3.3 Study population

The study population consisted of participants in Tromsø 7 who reported having previous MI (n = 753), previous PCI and/or CABG (n = 1226) and previous or current AP (n = 466). Some participants had more than one disease, making the total study population consist of 1483 participants.

In paper I, the study population was subdivided into these disease groups for some of the analyses: all participants reporting previous MI (n = 753), participants previous reporting PCI or CABG but not MI (n = 604) and participants reporting AP but not previous MI, PCI or CABG (n = 126).

3.4 Medication use for secondary prevention of CHD

We included medications recommended for secondary prevention of CHD based on the European Guidelines on cardiovascular disease prevention in clinical practice from 2012 (12). This included low-dose ASA, antihypertensive drugs (ACE-inhibitors, ARBs, beta-blockers, CCBs, thiazides and other antihypertensives) and LLDs (mainly statins).

3.4.1 Self-reported medication use from Tromsø 7 (Paper I and Paper II)

Self-reported current medication use for secondary prevention of CHD was based on questionnaire data from Tromsø 7. Current users of LLDs were defined as those answering "currently" to the question "Do you use, or have you used cholesterol lowering drugs?" or writing down the name of an LLD when asked to state the names of all the medications they had used regularly the previous four weeks. Users of antihypertensive drugs were defined as those answering "currently" when asked "Do you use, or have you used blood pressure lowering drugs?" or writing down the name of an antihypertensive drug. ASA-users were defined as those denoting a name for a medication containing ASA or answering "yes" when asked "If you have used analgesics and anti-inflammatory medication regularly in the past year - did you use "Baby" or low dose Acetylsalicylic acid (75 mg or 160 mg per tablet, i.e. Acetylsalicylic acid®/Albyl-E®/Asasantin Retard®)?".

Medication names were coded to their ATC-codes by trained personnel. The ATC-codes were used to categorize the medications from generic substances into the medication classes antihypertensive drugs and LLDs, and their subgroups; ACE inhibitors, ARBs, beta-blockers, CCBs, thiazides, other or unknown antihypertensives, and statins and other or unknown LLDs.

3.4.2 Medication use based on pharmacy dispensings from NorPD (Paper II and Paper III)

Current medication use was defined in three different ways in Paper II; one using a fixed-time window of 180 days, and two using legend-time methods assuming a daily dosage of either one dosage unit (usually one tablet) or one DDD. A fixed-time window of 180 days was chosen because LLDs, antihypertensive drugs and ASA are used chronically on a daily basis and dispensings for these types of medications typically give enough supplies to cover

approximately 90 days, and we also wanted to account for stockpiling and poor medication adherence. The assumption about a daily dosage of either one dosage unit or one DDD was made because the prescribed dosage was not available from NorPD. As the medications considered here are used daily with as little complicated regimen as possible, one dosage unit daily should be a fair assumption. We also performed the analyses assuming one DDD as this daily dosage should be the average dosage used for the individual generic substances, as stated in the definition of a DDD; "the assumed average maintenance dose per day for a drug used for its main indication in adults" (111). One dosage unit or one DDD has been assumed as daily dosage for these medications in some previous Nordic studies where prescribed dosage has not been available (68, 112).

Persistent prevalent medication users were defined in Paper III as participants using the relevant medications for more than 365 days before attending Tromsø 7, thereby excluding incident medication users who started using the medications during the 365 days before attending Tromsø 7 and non-persistent medication users who did not have any supplies of the medications available within 180 days before attendance.

3.5 Blood pressure and LDL-cholesterol measurements and treatment goals (Paper I and Paper III)

Blood pressure was measured with an automated digital device (Dinamap ProCare 300 monitor, GE Healthcare, Norway). Three consecutive measurements were taken with one-minute intervals and after two minutes of seated rest. Blood pressure was defined as the mean of the last two measurements. If only the third measurement was missing (n = 2), the second measurement was used. When both the second and third measurement, but not the first, was missing (n = 1), the first measurement was used.

LDL-cholesterol was collected and analysed by trained personnel using enzymatic colorimetric methods with commercial kits on a Cobas 8000 c702 (Roche Diagnostics GmbH, Mannheim, Germany) from non-fasting venous blood samples. The analysis was performed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway (ISO certification NS-EN ISO 15189:2012).

Treatment goals for blood pressure and LDL-cholesterol were defined in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice from 2012 (12) (see Table 1 in section 1.2.3). For blood pressure, the treatment goal was considered achieved if the participants had a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg, or, if they had diabetes, 80 mmHg. Treatment goal for LDL-cholesterol was considered achieved for participants who had an LDL-cholesterol of below 1.8 mmol/l.

3.6 Covariates (Paper I and Paper III)

Self-reported variables concerning age, sex, body mass index (BMI), relevant comorbidities, diet, physical activity, use of health services, alcohol consumption, smoking and use of smokeless tobacco were collected from the questionnaires in Tromsø 7. In Paper I these variables were used to calculate a propensity score which then was used to match participants using LLDs and antihypertensive drugs with participants who did not.

In Paper III the variables concerning alcohol consumption, smoking and use of smokeless tobacco, diet and physical activity were summarized in two variables containing gradients of lifestyle using multidimensional scaling.

3.7 Statistical analysis

3.7.1 Paper I

We used chi square tests to examine the relationship between achievement of both of the treatment goals for blood pressure and LDL-cholesterol and use of a combination of LLDs, antihypertensive drugs and ASA, and between achievement of both treatment goals and disease group.

Propensity score matched logistic regression was used to explore the association between use of antihypertensive drugs and achievement of treatment goal for blood pressure, and the association between use of LLDs and achievement of treatment goal for LDL-cholesterol. Propensity score matching is a method used to reduce bias by balancing the distribution of covariates between the exposed and unexposed groups (113). Due to the high number of missing replies in the covariates, multiple imputation was performed before propensity score

matching. This was done using multiple imputation by chained equations (MICE), a commonly used imputation method which can handle various variable types and skip patterns of questions in a survey (114). The imputation method was set based on the properties of the variables; predictive mean matching was used to impute numeric variables, logistic regression for binary categorical variables, proportional odds model for ordered categorical variables and polytomous logistic regression for unordered categorical variables. In the imputation process, more variables than those to be used in the propensity score matched logistic regression were included in order to improve the imputations. Taking into consideration the large dataset, amount of missing data in all variables and computer resources, ten imputed datasets were created with fifty iterations.

Descriptive statistics were done in SPSS version 25.0 for Windows (IBM Corp, 2017), while chi square test, multiple imputation and propensity score matched logistic regression were performed in R (R Core Team (2019)) using the packages mice and MatchIt.mice.

3.7.2 Paper II

Agreement between Tromsø 7 and NorPD was measured by percent observed agreement and Cohen's kappa. Cohen's kappa is the percent agreement corrected for chance. Agreement was considered poor for kappa-values <0.00, slight for kappa-values of 0.00-0.20, fair for kappa-values of 0.21-0.40, moderate for kappa-values of 0.41-0.60, substantial for kappa-values of 0.61-0.80 and almost perfect when kappa-values were 0.81-1.00, as described by Landis and Koch (115).

To determine the validity of the self-reported medication use, sensitivity and specificity were calculated using NorPD as the reference standard. Sensitivity was defined as the proportion of medication users defined by NorPD who were also defined as medication users by self-report (medication users in both sources divided by medication users in NorPD). Specificity was defined as the proportion of non-users defined by NorPD who did not self-report medication use (non-users in both sources divided by non-users in NorPD). Predictive values were also calculated. Positive predictive value (PPV) was the proportion of self-reported medication users who were also registered as users in NorPD (medication users in both sources divided by self-reported medication users) and negative predictive value (NPV) was the proportion

who were not self-reported medication users who were also not registered as users in NorPD (non-users in both sources divided by those not self-reporting medication use).

All analyses were conducted using SPSS version 25.0 for Windows (IBM Corp, 2017). Confidence intervals (CIs) were calculated in VassarStats (http://vassarstats.net/).

3.7.3 Paper III

Adherence was measured for persistent prevalent medication users as PDC, calculated as continuous multiple-interval measure of medication availability (CMA)7 using the R-package AdhereR (116). CMA7 is defined as "number of gap days for all event intervals extracted from the total time interval; (accounting for carry over from before the observation window and within the observation window, and excluding the supply left at the observation window end)" (116). The observation window was set to 365 days before attending Tromsø 7 until the attendance date, with a follow-up window from 01 January 2004 until 31 December 2016 which is the whole period from which we had information from NorPD.

Multivariable linear regression models were used to explore the association between non-adherence to LLDs, age, sex, lifestyle, BMI, current and previous diabetes and LDL-cholesterol and between non-adherence to antihypertensive drugs, age, sex, lifestyle, BMI, current and previous diabetes and systolic and diastolic blood pressure. Adherence was reversed and log-transformed (1.1 – log(PDC)) in the analyses because of the skewness in these variables. The analyses were done as complete case analyses, hence removing the participants with missing values in the relevant variables.

All analyses were performed using R (R Core Team (2021)) using the packages AdhereR and vegan.

3.8 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics of North Norway (2015/1775) and had an approved Data Protection Impact Assessment from UiT The Arctic University of Norway. The approvals are included in Appendix 4 and 5 (Norwegian only). All participants in the Tromsø Study have given written informed consent for their data to be used in research.

4 Results

4.1 Paper I

Among the total population with self-reported CHD in Tromsø 7, 72% reported using antihypertensive drugs, 76% LLDs, and 66% ASA. Use of both LLDs and ASA was reported by 59%, and 49% reported using all three medication groups. The use of all these medications was highest in participants who had had a previous MI and lowest in those who only had AP.

The treatment goal for blood pressure was reached by 58% of the study population. Achievement of the treatment goal was similar across the disease groups, but highest among participants with AP, where 62% had the recommended blood pressure, and lowest among those with PCI/CABG where the proportion was 56%.

Nine percent of the study population reached the treatment goal for LDL-cholesterol. Highest achievement of the treatment goal was found for participants with previous MI, where 11% had the recommended LDL-cholesterol, while the lowest achievement was found among those with only AP, where the proportion was 3%.

As so few participants reached the treatment goal for LDL-cholesterol, the proportion who achieved the treatment goals for both blood pressure and LDL-cholesterol was 6%.

There was a statistically significant association between using all three recommended medication classes and achieving both treatment goals. The proportion reaching both treatment goals was 9% among participants who used all three classes of drugs and 3% among those who did not use all three ($p < 0.001$). Hence adherence to prescription guidelines gave higher achievement of treatment goals.

There was also an association between CHD disease group and achievement of both treatment goals with the proportion reaching both treatment goals being 6% among participants with a previous MI, 6% among those with PCI and/or CABG and 1% among those with AP ($p = 0.04$).

Using LLDs was significantly associated with achieving the treatment goal for LDL-cholesterol (odds ratio (OR) = 14.0, 95% CI 3.6-54.7), but using antihypertensive drugs was

not significantly associated with achieving the treatment goal for blood pressure (OR = 1.3, 95% CI 0.7-2.6).

4.2 Paper II

Agreement between Tromsø 7 and NorPD for use of LLDs, antihypertensive drugs and ASA was substantial, with percent agreement over 80% for all medication groups, and kappa-values over 0.61. PPVs were high for all three medication classes, over 0.90 when using fixed-time window, which shows that when participants reported using these medications, the likelihood that they had them dispensed was high. Sensitivity was also high for all three main medication classes, indicating that a high proportion of those registered as users in NorPD also self-reported use of these medications in Tromsø 7.

Concerning the methods for defining current medication use in the NorPD, fixed-time window seemed to be the best with the highest kappa-values, specificity and positive predictive values; and sensitivity and negative predictive values comparable to the legend-time methods. Comparing the two legend-time methods showed that using the assumption of one unit a day generally gave higher values than assuming one DDD a day.

4.3 Paper III

Medication adherence was high. The average PDC was 0.94 for LLDs and antihypertensive drugs, and 0.97 for ASA. Eighty-eight percent of participants using LLDs, 92% of those using antihypertensive drugs and 95% of those using ASA had a PDC of 0.80 or higher.

Non-adherence to LLDs, female sex, lifestyle and current diabetes were significantly associated with increased LDL-cholesterol. Higher age was associated with increased systolic blood pressure, and lower age, male sex and lifestyle were associated with increased diastolic blood pressure.

5 Discussion

5.1 Discussion of main findings

5.1.1 Guideline adherence

Adherence to prescription guidelines was found to be relatively high in our study population, with 76% reporting using LLDs, 72% antihypertensive drugs and 66% ASA. However, this is lower than what has been found in previous studies, such as the STABILITY (STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY) (117) and CLARIFY (prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) (118) studies, the newest EUROASPIRE surveys (42, 43), and Norwegian studies such as NOR-COR (49) and the study by Halvorsen et al. from 2016 (47).

One reason for the lower guideline adherence in Tromsø 7 is the difference in study populations. Persons with CHD are in most studies included based on hospital records and within short time after their CHD event. The EUROASPIRE surveys recruited CHD patients from large academic hospitals and their follow-up occurred 6 months to 2-4 years after discharge (39-43). NOR-COR included CHD patients based on hospital discharge lists from the hospitals in Drammen and Vestfold within the last three years before the study (48), while the study by Halvorsen et al assessed medication use 12 months after MI (47). The STABILITY and CLARIFY studies both included persons with CHD from broader time perspective but had additional inclusion and exclusion criteria used to define their study populations, such as including patients only if they fulfilled at least one of these criteria: ≥60 years, having diabetes mellitus, low HDL-cholesterol, being a smoker, having renal dysfunction or polyvascular disease (117), or excluding persons that had been admitted to the hospital for CVD within three months before inclusion, or persons with serious conditions that may hamper their participation over time (118). Our study population was selected from a general population. There would therefore on average be a longer time span between the CHD events and participation in Tromsø 7 for the participants in our study than in the studies mentioned above. Among the participants in our study population who reported how old they were when they first had an MI (n = 636), PCI (n = 841), CABG (n = 497) or AP (n = 350), the time mean between the first CHD event and attendance in Tromsø 7 was 11.2 years for MI, 8.9 years for PCI, 10.3 years for CABG and 13.5 years for AP.

Persistence with medication therapy for secondary prevention of CHD is known to diminish over time (112, 119, 120), and our results could be a consequence of that. Persons with CHD in a general population are not studied to the same degree as CHD patients in the first years after their diagnosis. The need for studies investigating this population in long-term using population-based studies has been acknowledged (121). As the prevalence of CHD is increasing due to more persons surviving their initial CHD event, this is an important population to follow in a public health view, and our findings contribute to the field by increasing the knowledge about this population.

5.1.2 Validation of self-reported medication use

To assess guideline adherence to secondary prevention of CHD we used the participants' self-reported current use of LLDs, antihypertensive drugs and ASA. To examine if these responses corresponded with which medications were available to the participants, we performed the validation study comparing their responses with pharmacy dispensings from NorPD. We found substantial to almost perfect agreement for the three medication classes, with kappa-values of 0.81 for antihypertensive drugs, 0.78 for LLDs and 0.69 for ASA when using the fixed-time window method for defining current medication use in NorPD. This method gave higher agreement, positive predictive values and specificity compared to either of the legend-time methods and was our preferred method for comparison when it comes to these medications.

Our results are in line with previous studies comparing self-reported medication use and pharmacy dispensing data, especially for LLDs (61, 62, 69, 71, 72, 74, 75) and antihypertensive drugs (63, 64, 71-74, 76, 78). Comparing our results to studies that have examined the individual LLD and antihypertensive drug classes, our results are similar for statins (63, 65), ACE-inhibitors/ARBs (61, 62, 65, 66, 80), CCBs (61, 62, 65, 66, 81), thiazides (76, 80) and mostly also for beta-blockers (61, 62, 64-66, 80, 81). A Finnish study by Haapea et al. found only moderate agreement for beta-blockers with a kappa-value of 0.55 but this can be explained by the fact that not all beta-blockers are reimbursed, and the Finnish registry only contains information about reimbursed medications (67).

Our results concerning agreement and validity of self-reported ASA were lower than for LLDs and antihypertensive drugs. The results are comparable to what was found in studies

from New Zealand (63) and France (65), but lower than in two studies from Scotland (73) and Canada (79). This is surprising as low-dose ASA is only available on prescription in Norway but available OTC in most other countries. We therefore expected higher agreement and validity measures in our material than in similar studies from other countries, such as is the case with one Australian study (80).

Our results show PPVs over 0.90 for all medication groups and subgroups, thus indicating that we can be quite certain that the participants with CHD who report using these medications are actual medication users. NPVs are lower for some of the medications, particularly ASA and statins. We can therefore not be as confident that participants who do not report use of these medications are actual non-users.

For LLDs and antihypertensive drugs, sensitivity was high with values of 0.94-0.98, indicating that the Tromsø 7 questionnaire captures most of the users of these medications. Specificity was slightly lower, 0.88 for antihypertensive drugs and 0.78 for LLDs. No threshold exists for determining whether self-reported use of medications can be considered to be valid, and this has to be considered in each study situation (55). The implications the slightly lower specificity would have for Paper I are that some of the participants may have been misclassified as users of LLDs and antihypertensive drugs. This could have weakened the associations between use of LLDs and achievement of treatment goal for LDL-cholesterol and between use of antihypertensive drugs and achievement of treatment goal for blood pressure. The effect would however be expected to be small, as the proportion of participants that used LLDs and antihypertensive drugs was much larger than the proportion of non-users. The conclusion would not have changed, as the association between use of antihypertensive drugs and achievement of treatment goal for blood pressure was already found to be non-significant. The association between use of LLDs and achievement of treatment goal for LDL-cholesterol was strong, and even if some participants had been misclassified, most would have been correctly classified as LLD-users and the association would most likely have remained statistically significant.

5.1.3 Medication adherence

As we already found good adherence to prescription guidelines and that the reported medications used could be considered fairly valid, assessing how the medications are used

was the next step. We found a very high medication adherence for all three medication classes, with mean PDC of 0.94 for LLDs and antihypertensive drugs and 0.97 for ASA.

Adherence to cardiovascular medications is often found to be insufficient and lower than what we have found in this project (94, 122-125). Comparing studies examining adherence is complicated by the differing ways of measuring, calculating and defining adherence (126, 127). In our adherence study we have only looked at secondary prevention of CHD and only included prevalent persistent medication users in the implementation phase of the adherence process (84). These should be expected to have a high adherence. A study by Thornley et al. indicates this, by showing that 82% of the patients who had been dispensed statins three months before hospital admission had a statin dispensing ratio of ≥0.80 in the year after hospital discharge compared with only 44% of the patients who initiated statin treatment after the hospital admission (125).

Adherence to LLDs used for secondary prevention has been found to be higher than for primary prevention (128), and the same can be assumed for antihypertensive drugs and ASA. Our results are more comparable to studies that have investigated adherence to medications used for secondary prevention of CHD using dispensing data to define adherence by MPR or PDC, than studies that have included both primary and secondary prevention or used other methods for adherence measurements. Studies that have used MPR or PDC to assess adherence to medications used for secondary prevention of CHD report mean MPR or PDC values of 0.82-0.88 for LLDs, 0.91 for dual antiplatelet therapy (DAPT) and 0.33-0.84 for various antihypertensive drugs (122, 123). The proportion of persons with an MPR or PDC ≥0.80 was reported to be 76.5%-79.8% for LLDs, 88.1% for DAPT and 11.9%-52.7% for the various antihypertensive drugs (122, 129).

Non-persistence and poor implementation tend to be highest close to initiation of treatment (112). Persons that persist with treatment, generally have a higher implementation adherence. Medication adherence for secondary prevention is commonly measured in the first months or years after discharge from hospital after the CHD event. Not that much is known about medication adherence in persons with CHD in a general population with varying time since their CHD diagnosis. Ensuring that these persons persist with their medication therapy and have a high implementation adherence is essential to avoid new CHD events. Our results

therefore add to what is already known about medication adherence to secondary prevention of CHD.

Despite the high adherence to LLDs and antihypertensive drugs found in our study, few had reached the recommended treatment goals for LDL-cholesterol and blood pressure. Though sustaining a high medication adherence is important, these results suggest that initiating a complex and resource-demanding intervention to increase adherence in this population is probably inutile. Conversations with persons with CHD about the importance of adherence and their individual barriers to adherence could simply be conducted upon their visits to their GP's office or pharmacies.

5.1.4 Reduction of blood pressure and LDL-cholesterol and treatment goal achievement

In our study population we found that 58% had a blood pressure <140/90 mmHg (<140/80 mmHg if diabetic) and only 9% had an LDL-cholesterol <1.8 mmol/L. Achievement of the treatment goal for LDL-cholesterol was associated with using LLDs, and lower LDL-cholesterol was found to be associated with higher adherence to LLDs. This is in line with what has been found in the Norwegian NOR-COR study (130). Contrary to the results for LDL-cholesterol, the same associations were not seen for blood pressure, where there was no statistically significant association between using antihypertensive drugs and achieving the treatment goal for blood pressure, or any significant association between adherence to antihypertensive drugs and lower blood pressure. This finding also correlates well with findings from NOR-COR (131).

The proportion achieving the treatment goal for blood pressure in our study population is in line with what has been found in other studies. In the STABILITY study, 54% were found to have blood pressure control (blood pressure of <140/90 mmHg or 130/80 mmHg if diabetic) (117) and similar results were found for central and western Europe in the CLARIFY study (118). Kotseva et al. reported that 58% achieved the treatment goal for blood pressure in the newest EUROASPIRE study, EUROASPIRE V (43). The results from NOR-COR are also in accordance with ours with 54% of their study population reaching the treatment goal (49). The proportion achieving blood pressure control has been similar throughout all the EUROASPIRE surveys (39-43), with a small increase from EUROASPIRE III to EUROASPIRE IV (46). Results from previous waves of the Tromsø Study have demonstrated

that age-adjusted mean systolic and diastolic blood pressure in the general population had decreased from when Tromsø 2 was conducted in 1979-1980 to Tromsø 6 in 2007-2008 (132). Achievement of treatment goals for those with validated MI also increased. Among participants in Tromsø 4 who had a first-ever MI between 1994 and 2008, 46.2% had reached the treatment goal for blood pressure (<140/90 mmHg or <130/80 mmHg if diabetic) at participation in Tromsø 6 in 2007-2008, while among participants in Tromsø 6 who had a first-ever MI between 2007 and 2016, 52.7% had achieved the treatment goal at attendance in Tromsø 7 in 2015-2016 (133).

Consistent with our results, previous studies have found the treatment goal achievement for LDL-cholesterol to be lower than for blood pressure, however not as low as the 9% that was found in our study population. In EUROASPIRE V, 29% achieved the treatment goal for LDL-cholesterol of <1.8 mmol (43), while the proportion in the NOR-COR study was 43% (49). A higher proportion reached the LDL-cholesterol treatment goal in the STABILITY and CLARIFY studies. However, both these studies set the treatment goal for LDL-cholesterol at <2.6 mmol/L (117, 118).

Our results may partly be explained by our study population differing from those above, as mentioned in chapter 4.1.1. This may especially affect the comparison of achievement of the treatment goal for LDL-cholesterol, as the guideline recommendations have gradually lowered this treatment goal. Since most of the participants in our study population have had a coronary event several years ago, they may not have been followed up according to the newer guidelines. From 2019 a new and even lower treatment goal for LDL-cholesterol was presented. ESC/EAS guidelines for the management of dyslipidemias and ESC guidelines on chronic coronary syndrome now recommend an LDL-cholesterol of <1.4 mmol/L in addition to a reduction in LDL-cholesterol of ≥50% from baseline (14, 37). If this is to be obtainable, especially considering the low achievement of the previous treatment goal of <1.8 mmol/L, more effort needs to be focused on optimizing the existing treatment with LLDs.

5.1.5 How to improve medication therapy and treatment goal achievement among persons with CHD?

For persons with CHD to have an optimal treatment with LLDs and antihypertensive drugs, they need to start using these medications, keep using them and use sufficiently high dosages of the medications taken at correct time intervals. Though we have shown that both use of and

adherence to LLDs, antihypertensive drugs and ASA is high, there is always room for improvement.

According to the self-reported medication use in Tromsø 7, 24% did not use LLDs, 28% did not use antihypertensive drugs and 34% did not use ASA. The proportion defined as non-users in NorPD was similar for LLDs and antihypertensive drugs; 25% were defined as not having used LLDs and antihypertensive drugs at least one year before Tromsø 7. For ASA, the proportion of non-users was lower in NorPD, where 24% were defined as not having used ASA during the last year. Of the total study population, 12% did not have any dispensings for either LLDs, antihypertensive drugs or ASA, indicating possible non-initiators, while the remaining non-users at least one year before attendance in Tromsø 7 according to NorPD had at some point used these medications but discontinued treatment. Reasons for non-initiation and non-persistence should be explored and interventions to increase initiation and persistence are needed.

We have found high adherence among prevalent users persistent to the treatment regimen, however, this could still be optimized, especially for LLDs. Side-effects are commonly associated with suboptimal adherence and persistence. It is therefore important to discuss experienced side-effects with the patients and adjust treatment accordingly, either by change of medication or dosage, or by encouraging patients to attempt using the medications for a longer time if these are side-effects that are known to diminish over time.

To increase achievement of treatment goals for blood pressure and LDL-cholesterol, our results suggest that further optimizing medication adherence probably is not enough. Treatment of both blood pressure and LDL-cholesterol may need to be intensified. For treatment with LLDs this initially includes increasing dosages of statins, switching to more potent statins such as atorvastatin or rosuvastatin (134), or adding another LLD, i.e. ezetimibe (17). All patients may not reach the treatment goals, even with high dosages of the most potent statins in combination with ezetimibe, especially if the goal to reach is lowered to 1.4 mmol/L (135). New treatments to lower LDL-cholesterol include PCSK9-inhibitors. These have been shown to be effective, especially in combination with statins, and could be considered in cases where other treatments have failed. However, due to the high costs of PCSK9-inhibitors, they are currently not automatically reimbursed in Norway.

For antihypertensive drugs, the most recent recommendations are to start with combination therapy when hypertension is diagnosed, as combinations of several classes of antihypertensives is found to have a better effect compared to monotherapy (20). Adding a new antihypertensive drug from another antihypertensive class when treatment is insufficient is also found to be better than increasing dosages of preexisting antihypertensive drugs, to increase effect while avoiding intolerable side-effects. In our project, we found that 51% of those who reported using antihypertensive drugs, reported using antihypertensive drugs from more than one antihypertensive class. This shows great potential for optimizing treatment of hypertension by adding antihypertensive drugs from other antihypertensive classes. Resistant hypertension may still occur despite optimal treatment. Treatment with antihypertensive drugs from three different classes, usually an ACE-inhibitor/ARB combined with a CCB and a diuretic such as a thiazide, at the highest tolerable doses and optimal medication adherence without reaching recommended treatment goals is considered resistant hypertension (20). Patients with resistant hypertension are normally treated with additional antihypertensive drugs from other antihypertensive groups, most commonly an aldosterone antagonist. More research is still required to determine the effect and safety of other potential non-pharmacological treatments such as renal denervation or carotid baroreceptor stimulation, and these are therefore not usually recommended (20).

As most of this study population has not been diagnosed with CHD recently, they are generally followed up in primary care by their general practitioner (GP). Previous studies have found that many GPs lack knowledge about current treatment goals in secondary prevention of CHD (136, 137). This has also been seen in Norway, where GPs expressed lack of knowledge of treatment guidelines, strategies for adjusting medical treatment and how to handle side-effects, in addition to finding it challenging to reach the treatment goals, and talk to patients about it (138). Interventions targeting GPs therefore seems to have a great potential for improving secondary prevention of CHD.

Improved communication between hospitals and GPs concerning treatment follow-up after a CHD event could contribute to better follow-up of CHD patients. In the Norwegian study, GPs requested clearer instructions from the hospital to the GPs concerning optimal treatment including suggestions for titration of relevant medications and individualized treatment goals (138). This will likely aid the GPs in the follow-up of these patients.

To optimize treatment of CHD patients that have had their disease for a longer time, all GPs should be updated on the topic of secondary prevention of CHD. One possible method to achieve this could be a campaign as a part of the Norwegian Academic Detailing Program (KUPP) (139). The program is run by the Regional Drug Information and Pharmacovigilance Centers (RELIS) and the Clinical Pharmacological departments at the four university hospitals in Norway and is funded by the Ministry of Health and Care Services. The academic detailing is performed by trained pharmacists and physicians visiting GPs one-to-one in the GPs' offices. The sessions last about 20 minutes and the most important topics regarding medication use in specific therapeutic areas are discussed (139). Previous campaigns have included the topics non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, opioids for chronic pain, menopausal hormone therapy and treatment of diabetes type 2 (140). The academic detailing intervention on better use of NSAIDs resulted in a significant reduction in prescription of diclofenac and an increased prescription of naproxen (141), indicating that this is an effective intervention.

Closer collaboration between GPs and community pharmacists could also optimize patient care. Physician-pharmacist collaborative management has shown effect on blood pressure control among persons with hypertension and HbA1c reduction in diabetes patients (142). A study from Norway concluded that few GPs supported an active role for pharmacists and that to achieve an optimal collaboration between community pharmacists and GPs, the two professions' knowledge about each other needs to be increased (143).

Community pharmacists can contribute in the follow-up of medication treatment, especially in encouraging correct use of medications, and increase adherence and persistence. The intervention Medisinstart that was implemented and tested in Norwegian pharmacies in 2014-2015 was found to increase adherence to recently initiated medications for CVD (144). Medisinstart is offered to patients with a first-time prescription of an antihypertensive drug, LLD or anticoagulant drug and consists of two consultations with a pharmacist focusing on correct use of the new medication and how to handle side-effects and forgotten dosages. A randomized controlled trial assessing the effect of the intervention found an increase in self-reported adherence and decreased concerns about medications (144). The effect was strongest for statins. Though this service is only offered to new medication users, there is a potential for offering such services for prevalent medication users. Pharmacies can also offer support and

recommendations for lifestyle modifications such as smoking cessation and weight loss which are also important factors in secondary prevention of CHD.

5.2 Methodological challenges

A study's validity is influenced by measurement errors. These measurement errors can be either random or systematic. Both the internal and external validity of a study will vary depending on the degree of particularly systematic errors.

5.2.1 Random error

Random error is the proportion of variance in a measurement that is not connected to any other variables and can be regarded as happened by chance (145). While systematic errors will distort estimates and associations in a particular direction, random error affects all subgroups non-differentially (146). Random error is more likely to affect the study's power, thus making it more difficult to demonstrate associations that truly exist, but this can usually be controlled for by including a sufficient number of measurements.

Analyses of LDL-cholesterol and HbA1c in our study could have been subject to smaller measurement errors, but as the same equipment, procedures and laboratory were used, these would most likely be random errors and not affected by systematic bias. In the first five waves of the Tromsø Study, LDL-cholesterol was calculated from Friedewald's formula, while in Tromsø 7, it was measured by direct enzymatic colorimetric methods. We became aware of this change after the publication of Paper I, and a correction has been published to that effect (147). The use of direct enzymatic colorimetric methods is an advantage, as the use of Friedewald's formula has been shown to underestimate the true LDL-cholesterol concentration (148), thus rendering our results more reliable.

5.2.2 Internal validity

Internal validity describes to which degree the study is free from systematic error (145), and thus whether the study results apply to the study population. The methods used to select the study population, collect information and conduct the analyses affect the internal validity of a study. Internal validity also depends on identification and measurement of potential confounders and choice of exposure windows (145).

Selection of the study population

The study population in this project consisted of participants in Tromsø 7 who self-reported previous MI, PCI, CABG and/or AP (n = 1483). Self-reported diagnoses could be biased, hence the validity of the true disease status of our study population may be questioned. To attempt to validate our study population, it was possible to compare it to a local CVD registry existing in connection to the Tromsø Study. This registry contains information about participants with certain or probable previous MI based on their medical journal. According to this registry, 670 of the 753 (89%) who reported an MI in our study, were registered with a previous MI. Among our total study population (n = 1483), 1186 participants (80%) were included in the registry. Since the registry only includes cases with certain or probable MI, all participants with PCI, CABG or AP cannot be expected to be registered. These participants could still have CHD, even though they have not had an MI.

The local CVD registry is limited by not being completely updated at the time we received the data from it. The registry also only includes data from the University Hospital of North Norway, and myocardial infarctions treated at other hospitals are not included. This implies that not being registered in the CVD registry does not exclude having a true MI diagnosis.

Comparison with the local CVD registry makes us fairly sure that the participants in our study population are persons with CHD. However, there may be more participants in Tromsø 7 with a CHD diagnosis than those we included. This is probably not a major issue, as severe diagnoses such as CHD are more likely to be recalled, and also not as sensitive as e.g. mental disorders or sexually transmitted diseases, and hence more likely to be reported by the participants (55).

A recent study by Hopstock et al. investigated treatment goal achievement and use of medications for secondary prevention among persons with validated MI and/or stroke who had participated in Tromsø 7 and at least one of the previous six waves or the Tromsø Study (n = 904) (149). They found that 55.2% achieved the treatment goal for blood pressure and 9.0% the treatment goal for LDL-cholesterol, while 75.9% used antihypertensive drugs and 81.0% LLDs. Their study population should be partly overlapping with ours, but with cases validated in the local CVD registry, and also including participants who have had a stroke and excluding cases with only PCI, CABG or AP. As their results are very similar to ours, we

would likely that have gotten the same results if we had included persons with validated instead of self-reported CHD.

Collection of information

Information bias

Information bias derives from systematic differences in the collection, recall, recording or handling of information and is common in observational studies, especially those using self-reported data (150). The major types of information bias include recall bias, reporting bias and observer bias (150).

Recall bias occurs when participants do not accurately remember past experiences or events and hence do not report them correctly (145, 151). This could lead to systematic errors as poor recall may be more common among some participants than others, such as the elderly, less educated or those with lower socioeconomic status (151). Self-reported medication use may have been underestimated in Paper I due to recall bias, but the problem is found to be smaller for medications used regularly such as medications used for secondary prevention of CHD, compared with medications used as needed (55). The results from the validation study (Paper II) also indicated that this is of minor concern. Recall bias could also have affected the selection of the study population as discussed above, and if so, may have affected the external validity of the study.

Reporting bias can be defined as selectively revealing or suppressing information or study results (145). It is most commonly used to describe scientific misconduct, for instance by not publishing negative results (152), but the term reporting bias also refers to the situations in which participants in a study select whether or not to report particularly sensitive information such as sexual experiences or medical history (145). Self-reported lifestyle measures such as diet, smoking, alcohol consumption and physical activity could be affected by reporting bias. Smokers may hesitate to admit that they smoke or how many cigarettes they smoke daily. Participants may also estimate that they have a healthier diet and exert more physical activity than they actually do.

Observer bias occurs when there is a systematic difference between a true value and an observed value because of the failure of an observer to measure a phenomenon accurately (145, 153). This could happen when a measurement is dependent on subjective judgement

which could vary between observers, and if the differences are systematic this could introduce bias. Inadequate training in the use of measurement devices could introduce such bias (153). In the Tromsø Study, measurement of height, weight and blood pressure could potentially be affected by this, however, the impact should be low as the personnel conducting the examinations have been trained and follow standard procedures.

Blood pressure measurement could also be affected by apprehension bias. Apprehension bias occurs when a study participant responds differently when being observed (154). White-coat hypertension is a well-known example of this effect (155). Going through a health examination could make the participants anxious which in turn could raise the blood pressure, thus giving recorded measurements higher than their normal blood pressure. This could potentially have led us to overestimate blood pressure and hence underestimate the proportion reaching the blood pressure treatment goal.

Missing data

Information bias can be introduced depending on the handling of missing data (150). Missing data happens as a result of participants not answering all the questions in a questionnaire or not completing clinical examinations. Of the data sources used in this project, missing data is mainly a problem in the data from the Tromsø Study.

The pattern of missing data is usually classified as missing completely at random, missing at random and missing not at random. Missing completely at random indicates that there are no systematic differences between missing values and the observed data (145). Data is missing at random when the systematic difference between missing and observed data can be explained by differences in observed data, e.g. if missingness in a question about depression is higher among male participants without being dependent on their depression status. In the case of data missing not at random, there are systematic differences between the missing and observed data that cannot be explained by the observed data (145), e.g. if missingness about depression is highest among the most depressed participants.

Analyzing datasets with missing data can be handled by either excluding participants with missing data or imputing values for the missing data (156). In this project, both methods were used. Analyses in paper III were done as complete-case analyses, meaning that participants with missing values in the variables used for the analyses were not included. This may have

induced bias if the participants with missing data were different from those with complete data. It also leaves us with a smaller study population and loss of precision. However, the proportion of participants with missing data was about 10%, so not very large and should not greatly reduce the validity of our results (156).

Multiple imputation was done in Paper I for variables used to calculate the propensity score. This is a method that retains the uncertainty about the missing data by creating several datasets with several imputed values for the missing data (114). To attempt to avoid inducing bias in the multiple imputation analyses, we included as many variables as possible in the imputation model. All variables that were available to us in the dataset from Tromsø 7 were included if the proportion of missing in the variable was less than 50%. Higher proportions of missing than this led to difficulties completing the multiply imputed datasets using the mice package in R. All variables included in the multiple imputations were reported in the supplementary of Paper I.

For some variables used throughout the project, single imputation was also used where the imputed value seemed reasonable. In both Paper I and Paper III, participants were assumed to have diabetes if they reported using any antidiabetic drug. Those not reporting having diabetes nor reporting use of antidiabetics were considered to not have diabetes in Paper III, while in Paper I this was subject to multiple imputation. Use of LLDs, antihypertensive drugs or ASA was coded as "no" if the data was missing. This is because we included both prespecified and open-ended questions to determine medication use, and not reporting any medications in the open-ended question indicated no use of these medications.

For variables concerning smoking, alcohol consumption and use of health services, we combined several variables concerning the same issue to reduce the amount of missing data. An example is that if participants reported current smoking on any of the three variables concerning smoking, they would be considered a current smoker. Similarly, if participants did not report current smoking but previous smoking, they were considered previous smokers. When the remaining participants reported never having smoked, they were considered non-smokers.

Missing data is generally not a problem in the data from NorPD. The only cases in which this could be a problem is when the personal identification number is missing and linking

therefore is impossible. This is a minor problem as it occurs very rarely. Proportions of prescriptions without a valid personal identification number has decreased from 3.7% in 2004, through 2% in 2005-2007 and 1.4% in 2008-2009, to less than 1% in 2010-2017 (157). This could potentially have led us to underestimate validity of medication use and medication adherence but has most likely not affected our results at all.

Statistical methods

Propensity score analysis

Propensity score analysis methods are used to reduce bias in effect estimates in observational studies (158). The propensity score is calculated as the probability of the exposure based on the included covariates. Different propensity score methods can be used to balance the covariate distributions between the exposed and non-exposed in an analysis, the most common being matching, inverse probability of treatment weighting, stratification and covariate adjustment using the propensity score (158).

Compared to multivariable regression where covariates are adjusted for by including them in the regression analysis, propensity score analyses have some advantages. One is that the balancing of covariates is done separately from the outcome analysis and is therefore performed independently and without knowledge of the outcome (113). Another advantage is that propensity score allows for more variables to be included as covariates than what is recommended in normal regression analyses, and thus fewer covariates needs to be included in the outcome analyses. And lastly, the included covariates need not be assumed to be confounders as all variables that are assumed to affect the outcome could be included in the propensity score, irrespective of whether they also affect the exposure (113).

Some challenges were encountered during the analyses. Due to the high proportion of users of LLDs and antihypertensive drugs, the matching process could not be done in a one-to-one ratio, as that would have led us to exclude too many of the participants using the medications. The best solution was therefore to do the matching with replacement, thus allowing the non-users to be matched with several of the medication users. This could have introduced bias, so we performed a sensitivity analysis using a one-to-one matching, which did not substantially change the results. Another challenge encountered was that covariates may not have been completely balanced, in particular between users and non-users of antihypertensive drugs.

After matching the standardized mean difference (SMD) is recommended to be lower than 0.1 (159) or at least lower than 0.25 (160). For some covariates in our analysis, SMDs were larger than this. In retrospect, we should have considered including these covariates in the outcome analysis as well as in the propensity score in order to completely adjust for them. The covariate that had the highest SMD values was age. This indicates that the users of antihypertensive drugs were older than non-users. In Paper III we found that older age was highly significantly associated with higher blood pressure. If we had included age as a covariate in our outcome analysis in Paper I, it would therefore most likely have diminished the association between use of antihypertensive drugs and achieving the treatment goal for blood pressure. As this association was found to be small and not statistically significant, it would not have changed the result substantially.

Agreement measures

Agreement between two information sources can be calculated by different measures. In Paper II we chose to report both percent agreement and Cohen's kappa. Cohen's kappa is the most commonly used measure to determine agreement between self-reported medication use and dispensing data from pharmacies, and by using this, our results could be compared with other studies. Though commonly used, the method does have some flaws. The kappa statistic is sensitive to prevalence and bias, leading to kappa paradoxes which give artificially low kappa coefficients (161). Adjusted versions of Cohen's kappa have been developed, such as prevalence-adjusted bias-adjusted kappa (PABAK) (162), and this measure has been used in some studies but to a limited degree. Its superiority to the normal Cohen's kappa statistic is also debatable (163). In Paper II we supplied both percent agreement and the numbers of medication users in both sources, neither sources and either one of the sources, making it possible for readers to calculate any other agreement measure.

Proportion of days covered

Pharmacy dispensing data is one of the most commonly used data sources for determining adherence. PDC is one of the most used adherence measures based on pharmacy dispensing data and is calculated as the sum of the days covered with medication supplies divided by the number of days in the observation period (89). Though it is sometimes used interchangeably with MPR or MPR capped at one, there are differences in these two measures. MPR is defined as the sum of the days' supply for all prescription fills in the observation period

divided by the number of days in the period (89). Contrary to PDC, this implies that MPR can exceed 1, as the sum of the days' supply can be larger than the number of days in the period unlike the number of days covered which cannot be more than the total number of days in the period. Another limitation with MPR is that it may allow for retroactive compensation, meaning that as the formula for MPR adds together all supplies in the period, this may allow for oversupply later in the period to compensate for gaps early in the period (164) which would overestimate the adherence measure. PDC is based on treatment episodes, and only take into consideration medications available from the day they have been dispensed at the pharmacy (89).

As with other adherence measures based on pharmacy dispensing data, PDC also has some limitations. First, we can only assume that the dispensed medication is actually ingested. Also, since PDC represents the average adherence over the chosen time period, we cannot determine when the missed doses occurred or if the doses were taken on time (e.g. in the morning) (85). Missing several consecutive doses could have a worse treatment outcome than missing the same number of doses spread out over time. Using a set observation window rather than a period between a set first and last dispensing also complicates the interpretation of a low PDC-value. It makes it more difficult to know whether the low value is caused by poor implementation adherence or non-persistence (164). In our analyses we chose to handle this by excluding participants with no supplies available the last 180 days of the observation window to ensure that we mainly were capturing poor implementation adherence without influence of non-persistence. This also correlates with the definitions from Paper II, where participants without any medications dispensed within 180 days before attending Tromsø 7 were considered non-users of the medications.

Our observation window was set to one year before attendance in Tromsø 7 to assess adherence before the measurements of blood pressure and LDL-cholesterol, and to include enough dispensings to get a reliable measure of PDC. Vollmer et al found that at least 9 months of dispensing is needed for this when the average supplies from one dispensing covers 2-3 months (165). Incident medication users thus had to be excluded.

Since we cannot be certain that the dispensed medications are actually taken, PDC will only provide an estimate of the maximal possible level of adherence based on medication

possession. Our calculation of PDC based on NorPD may therefore have overestimated the true medication adherence. However, compared to using the two questions regarding medication non-adherence available in Tromsø 7, our results showed lower adherence. One of the questions in Tromsø 7 asked "How many times a week do you forget to take your medicines?" and the other "How many times a week do you decide to miss out your medicines?". Of the 1151 (77.6% of the total study population) who answered the first question, 97.3% answered that they forget to take their medications one time a week or less, which is comparable to less than 80% of the time. For the second question, of the 1120 (75.5% of the study population) who answered the question, 99.1% said that they decided to miss out on their medications once a week or less. This indicates even higher adherence than what was estimated based on NorPD, in accordance with previous research showing that self-reported adherence tend to overestimate actual adherence (166). These questions would however give an indication of whether non-adherence was intentional or not, which is not possible to explore using pharmacy dispensing data.

Confounding

Confounding occurs as a result of a factor being independently associated with both exposure and outcome, thus potentially causing distorted associations (167). Observed confounded associations could thereby be partially or completely explained by these factors, called confounders. Confounders arise when there are mutual causes of the studied exposure and outcome (145). To attain valid results, confounders must be adjusted for. The best way to reduce confounding is through randomization (167). However, as this is not possible in observational studies, confounders have to be controlled for in the analyses, most commonly through stratification or multiple-regression techniques (168). In paper I we controlled for confounders by using propensity score matching, and in paper III through multivariable regression. As in all observational studies, there is however always a possibility of there being other unmeasured confounders that have not been accounted for.

5.2.3 External validity

External validity, or generalizability, is described as the degree to which the results of a study can be applied to populations that did not participate in the study (145). If a study is externally valid, unbiased inferences can be made regarding other specific populations beyond the participants in the study. By some definitions, extrapolating results from a study to a

population, in which the population systematically differs from participants in the study, is considered as selection bias. A more correct definition of selection bias rather imply a lack of internal validity, by describing selection bias as an association between an exposure and an outcome influenced by the procedures used to select individuals into the study or analysis. If this selection conditions on a factor that is affected by, or a cause of, the exposure and the outcome, selection bias could arise (145). This type of selection bias is usually not a major issue in cross-sectional studies based on general population health surveys such as the Tromsø Study.

Generalizability or external validity implies to which degree the population studied is sufficiently similar to other populations to be representative for these populations.

The population invited to participate in the Tromsø Study are inhabitants in the municipality of Tromsø. The municipality includes a university town and had about 73 000 inhabitants at the time Tromsø 7 was conducted. Enrollment in the Tromsø Study has differed between the different waves conducted. In Tromsø 7, all inhabitants ≥40 years (n = 32 591) were invited to participate and 65% (n = 21 083) attended. Though this is a fair attendance rate compared to other health surveys (169), that almost one third of the invitees chose not to attend could give rise to concern. More women (67.0%) attended Tromsø 7 compared to men (62.4%) and attendance was highest in the age groups between 60 and 75 years (109). In previous waves of the Tromsø Study it has been seen that non-attendees are more likely to be younger, male and single compared to those who do attend (170). There are also indications that persons that have participated in more than one of the waves may have lower mortalities than non-attendees. This is in line with what has been found in another similar Norwegian health survey, HUNT (171). In the HUNT study they also found that non-participants had higher prevalences of CVD, diabetes and psychiatric disorders, in addition to lower socio-economic status and higher mortality (172). This is likely to also apply to the Tromsø Study. Our study population may therefore be slightly healthier than general CHD populations. As the study population is based on self-report, the participants may also be more conscious of their own disease than the general CHD population. Validity of CHD in the study population was discussed in chapter 5.2.2.

Previous waves of the Tromsø Study have considered it representative for a Northern European, urban, Caucasian population (173). Our study population consisted of persons with CHD. Non-participation and possible non-survival of those with poorest health indicate that our results may need to be restricted to relatively healthy persons living with a diagnosis of CHD. Access to and affordability of medications and other health care resources varies between countries, hence our results are probably more relevant for countries with similar health care systems as Norway, such as the other Nordic and possibly Northern European countries.

5.3 Ethical considerations

Informed consent is of great importance when conducting medical research. When participating in research projects, potential participants should be given adequate information about the study and its potential harms and benefits (174). Participation in the Tromsø Study supplied benefits for the participants by providing them with some results of their examinations, including height, weight, BMI, hemoglobin, blood pressure, cholesterol and if the results indicated that they may have diabetes. If any test results showed the need for further follow-up of GPs or specialists, this would be mentioned and reference to a specialist would be provided. With the invitation to participate in Tromsø 7 a comprehensive study information brochure was included (see Appendix 1). The brochure included information both about which tests would be performed and how the data would be handled. It also mentioned the potential for linkage to other registries, including NorPD. At attendance, participants signed a written informed consent based on the information in the brochure. This consent can be retracted at any time at the participants' request. Tromsø 7 has been approved by Regional Committee for Medical and Health Research Ethics of North Norway (2014/940).

NorPD is a pseudonymized health registry containing information about all dispensed prescriptions from Norwegian pharmacies to individuals (110). This information includes the individuals' sex and age. Pseudonymization implies that name and national personal identity number are replaced by a pseudonym. This pseudonym makes it possible to follow individuals over time and link it to other data sources without knowing the individuals' identity. Statistics Norway is responsible for the pseudonymizing process, and when linking NorPD with other data sources they provide the key used for the linking of the individuals' data to avoid identification (110). Registration in NorPD is mandatory and not based on

informed consent. Withdrawal is not possible, but each individual has the right to access the information registered about themselves. Though registration in health registries like NorPD may not benefit each individual directly, it is important for attaining valid research results for the whole population. Valid research based on complete health registries is used to improve health care, which will benefit all individuals.

6 Conclusion

The project results showed that adherence to medication therapy for secondary prevention in persons with CHD in a general population was high, but achievement of treatment goals for blood pressure and especially LDL-cholesterol was low. Use of, and adherence to, LLDs was statistically significantly associated with achieving the treatment goal for LDL-cholesterol and with lower LDL-cholesterol. Similar associations were not found between use of or adherence to antihypertensive drugs and achieving the treatment goal for blood pressure or lower systolic or diastolic blood pressure.

This implicates that treatment of LDL-cholesterol could be optimized by ensuring that all CHD patients that are eligible for LLD treatment should initiate such treatment and be encouraged to adhere to the prescribed therapy. As so few reach the treatment goal for LDL-cholesterol this will probably be insufficient to reduce LDL-cholesterol to the recommended level. More intensive treatment of both hypertension and hypercholesterolemia is most likely needed. However, this should be further explored in future research.

Our results show that most persons with chronic CHD follow the treatment they are prescribed. A potential intervention to improve secondary prevention to CHD should probably be aimed at the prescription level, making sure that these persons receive treatment optimal to reach the recommended treatment goals. This may be achievable through education of and reminders to general practitioners and enhanced collaboration between health personnel, both between primary and secondary care, and within primary care.

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Paper I

BMC Cardiovascular Disorders

RESEARCH ARTICLE

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Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7

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Abstract

Background: Adherence to clinical practice guidelines for coronary heart disease (CHD) reduces morbidity, mortality and treatment costs. We aimed to describe and compare adherence to prescription guidelines for persons with CHD, and explore its association with treatment goal achievement.

Method: We included all participants reporting myocardial infarction, angina, percutaneous coronary intervention and/or coronary artery bypass surgery in the seventh wave of the Tromsø Study (2015–2016, n = 1483). Medication use and treatment goal measures (blood pressure, low-density lipoprotein (LDL)-cholesterol and HbA1c) were compared to clinical practice guidelines on secondary CHD prevention. Propensity score matched logistic regression was used to assess the association between the use of antihypertensive drugs and achievement of treatment goal for blood pressure, and the use of lipid-lowering drugs (LLDs) and achievement of treatment goal for LDL-cholesterol.

Results: The prevalence of pharmacological CHD treatment was 76% for LLDs, 72% for antihypertensive drugs and 66% for acetylsalicylic acid. The blood pressure goal (< 140/90 mmHg, < 140/80 mmHg if diabetic) was achieved by 58% and the LDL-cholesterol goal (< 1.8 mmol/l or < 70 mg/dL) by 9%. There was a strong association between using LLDs and achieving the treatment goal for LDL-cholesterol (OR 14.0, 95% CI 3.6–54.7), but not between using antihypertensive drugs and blood pressure goal achievement (OR 1.4, 95% CI 0.7–2.7).

Conclusion: Treatment goal achievement of LDL-cholesterol and blood pressure was low, despite the relatively high use of LLDs and antihypertensive drugs. Further research is needed to find the proper actions to increase achievement of the treatment goals.

Keywords: Coronary heart disease, Prescription guidelines, Blood pressure, Antihypertensive agents, Lipid-lowering drugs, Low-density lipoprotein (LDL)-cholesterol

Background

Coronary heart disease (CHD) is one of the leading causes of deaths worldwide and a common cause of hospital admissions [1, 2]. The major modifiable risk factors are high blood pressure and cholesterol levels, tobacco smoking, diabetes mellitus, low physical activity, obesity, and unhealthy diet [3]. Over the recent decades,

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the world has witnessed a substantial reduction in CHD morbidity and mortality which is partially attributed to strategies based on lowering of blood pressure and cholesterol, as well as successful acute treatment [4, 5].

Clinical practice guidelines for CHD promote risk factor reduction, both in terms of lifestyle changes and medication use. Lipid-lowering drugs (LLDs), antihypertensive drugs and acetylsalicylic acid (ASA) comprise the recommended secondary prevention after both myocardial infarction (MI) and coronary artery intervention like percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) [6]. Adherence to these prescription guidelines has been shown to prevent premature mortality, reduce morbidity and healthcare costs, and improve the patient's quality of life [6].

The European survey of cardiovascular disease prevention and diabetes (EUROASPIRE) is the largest European CHD survey, and it has evaluated the implementation of clinical guidelines in CHD patients five times since 1995–1996 [7]. The most recent EUROASPIRE survey showed that > 80% of CHD patients use antihypertensive drugs and LLDs. The survey also showed that achievement of the recommended treatment goals is low, where 58% of the patients reach the treatment goal for blood pressure and 29% the treatment goal for low-density lipoprotein (LDL)-cholesterol. Similar results have also been found in a Norwegian study, where 93% used both antihypertensive drugs and LLDs, while 54% reached the treatment goal for blood pressure and 43% reached the treatment goal for LDL-cholesterol [8].

Studies have shown an increase in treatment goal achievement in line with a decrease in blood pressure and cholesterol in the general population [9–13], but mainly describe adherence to clinical prescription guidelines and treatment goal achievement on an aggregated and not an individual level. Associations between treatment goal achievement and adherence to guidelines concerning prescription have also not been explored.

The aim of this study was to describe and compare adherence to prescription guidelines for persons with CHD and explore its association with treatment goal achievement for blood pressure and LDL-cholesterol.

Methods

Study setting and study population

The Tromsø Study is a Norwegian population-based epidemiological health study that has been conducted seven times from 1974 to 2016 [14]. The population of the Tromsø Study consists of inhabitants in the municipality of Tromsø in North Norway, a university town with approximately 70 000 inhabitants, and it is considered representative for a white, urban Northern European population [15].

The current study is a cross-sectional study applying data collected from participants in the seventh wave of the Tromsø Study (Tromsø 7). Tromsø 7 was conducted in 2015 and 2016 and invited all inhabitants in the municipality aged 40 years or older (n = 32,591) to participate. Response rate was 65% (n = 21,083). Participants answered several questionnaires, donated blood samples and went through a range of anthropometric measurements (height, weight, body circumferences and clinical examinations). Links to the questionnaires can be found at the Tromsø Study's webpage [16]. We included persons who self-reported CHD in the mandatory questionnaire, i.e. previous MI, present or previous angina pectoris (AP) and/or previous PCI or CABG. Participants with self-reported diabetes or reporting use of antidiabetic drugs and those with self-reported hypertension were defined as subgroups in some analyses.

We included a total of 1483 (7.0%) participants with CHD; 753 with previous MI, 466 with AP and 1226 with previous PCI and/or CABG, some of them indicating more than one disease (Fig. 1). We divided our study population into three subgroups; previous MI (n = 753), PCI or CABG but no previous MI (n = 604) and only AP with no previous MI, PCI or CABG (n = 126). Of the 1483 participants with CHD, 214 (14%) had diabetes, and 827 (56%) reported having hypertension.

Data extraction

We extracted information about blood pressure measurements from clinical examinations, LDL-cholesterol and HbA1c from blood samples and self-reported data from questionnaires. The questionnaire data included information about present and previous diseases, medication use, health concerns, use of health services, diet, physical activity, smoking status, alcohol consumption and socio-demography.

Prevalent users of LLDs, antihypertensive drugs and antidiabetic drugs were defined by two approaches; (1) by including those who replied "currently" when asked "*Do you use, or have you used cholesterol lowering drugs/blood pressure lowering drugs/insulin or tablets for diabetes?*" (answering options were "currently", "previously, not now" and "never used") or (2) mentioning the brand name of medications within these drug classes when asked to write down the brand names for all medications used regularly during the previous four weeks. Prevalent ASA use was defined as answering "yes" when asked *"If you have used analgesics and anti-inflammatory medication regularly in the past year—did you use "Baby" or low dose acetylsalicylic acid (ASA) Acetylsalisylsyre® Albyl-E® Asasantin Retard® (75/160 mg per tablet)?"* (answering

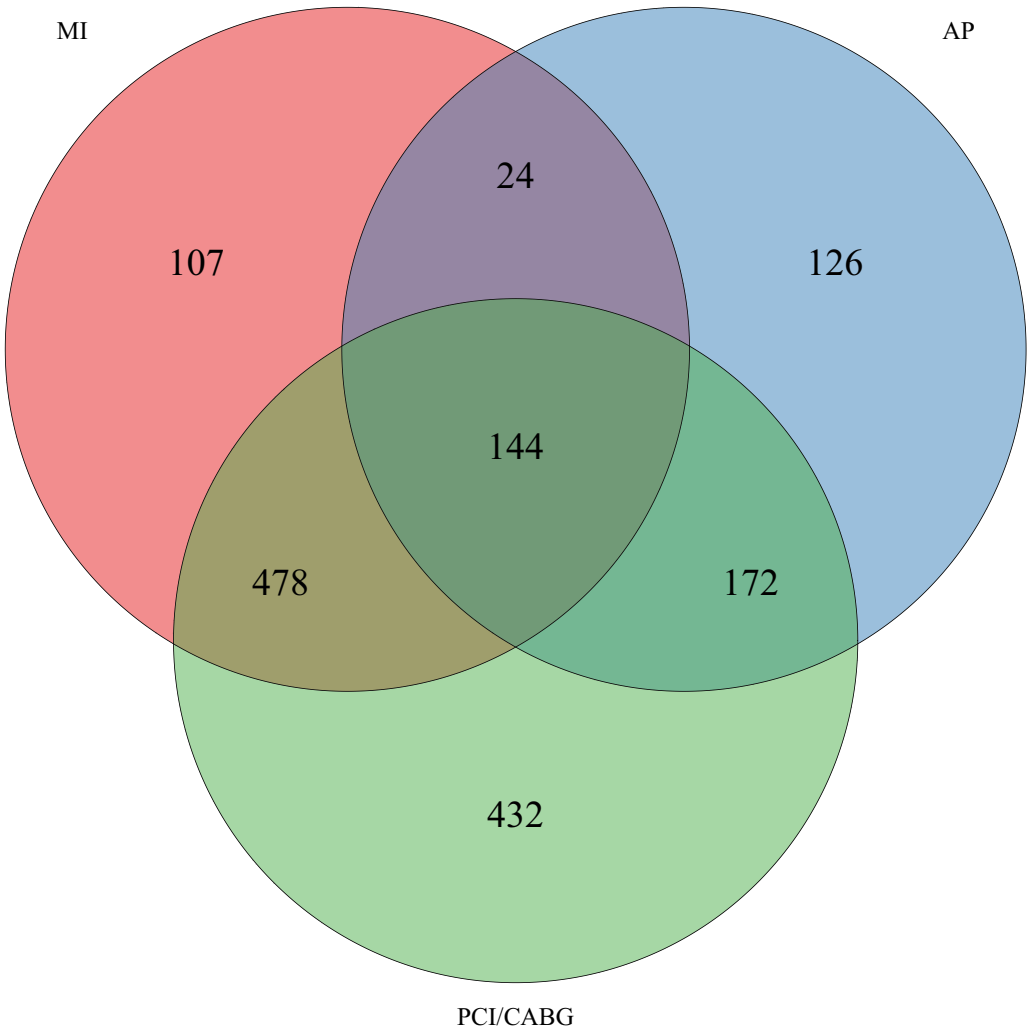

Fig. 1 Distribution of participants across coronary heart disease groups in Tromsø 7. AP, angina pectoris; CABG, coronary artery bypass surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention

options were "yes" and "no"), or mentioning a brand name for ASA when asked to write down brand names for all the medications used regularly during the previous four weeks.

Brand names were recoded by trained personnel using the anatomical therapeutic chemical (ATC) classification system and categorised into medication groups. LLDs included statins and other LLDs. Antihypertensive drugs included angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), thiazides, other diuretics and other antihypertensives (Additional file 1: Table S1).

In Tromsø 7, blood pressure was measured with an automated digital device (Dinamap ProCare 300 monitor, GE Healthcare, Norway) [9]. Three consecutive measurements were taken. Blood pressure was defined as the mean of the last two measurements. If only the third measurement was missing (n = 2), the second measurement was used. When both the second and third measurement, but not the first, was missing (n = 1), the first measurement was used. LDL-cholesterol was collected and analyzed by trained personnel using enzymatic colorimetric methods with commercial kits on a Cobas 8000 c702 (Roche Diagnostics GmbH, Mannheim, Germany) from non-fasting venous blood samples. The analysis was performed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway (ISO certification NS-EN ISO 15189:2012) [10].

Treatment goal achievement and medication use were assessed based on the European Guidelines on cardiovascular disease prevention in clinical practice from 2012 (Table 1) [6]. At the time of data collection, there were no Norwegian clinical guidelines for secondary prevention of CHD.

Statistical method

Descriptive statistics are presented as frequencies with proportions (%) (categorical variables) and means with standard deviation (SD) (continuous variables).

Chi square tests were used to examine the relationship between achievement of treatment goals for blood pressure and LDL-cholesterol and use of LLDs, antihypertensive drugs and ASA, and between achievement of treatment goals and disease group. Significance level was set to 5%.

Logistic regression was used to explore the association between use of antihypertensive drugs and achievement of treatment goal for blood pressure, as well as the association between use of LLDs and achievement of treatment goal for LDL-cholesterol. Participants with missing measurements for blood pressure (n = 3) and LDL-cholesterol (n = 11) were excluded from the respective analyses. Propensity score matching was used to control for confounding from covariates including age, sex, body mass index (BMI), relevant comorbidities, diet, physical activity, use of health services, alcohol consumption and smoking (including use of smokeless tobacco) (for more information about the variables included, see Additional file 1: Table S2). The matching method used was nearest neighbour matching, and the procedure was performed with replacement and a caliper of 0.2.

Due to the high proportion of missing values in some of the covariates, imputation was needed to perform the analyses. If a factor was described by more than one variable (e.g. use of health services, tobacco, alcohol), these variables were combined. For instance, a participant reporting current smoking on at least one question regarding smoking habits would be categorised as a smoker. Multiple imputation by chained equations was then performed using the R packages mice and MatchIt.mice (see Additional file 1: Table S3 for variables included). Predictive mean matching was used to impute numeric variables, logistic regression for binary categorical variables, proportional odds model for ordered categorical variables and polytomous logistic regression for unordered categorical variables. Ten imputated datasets where created with 50 iterations. The analyses were then performed with the within approach, which means that the propensity score matching and logistic regression was performed in each imputed dataset and the results subsequently pooled together to an overall result. We used the non-imputed dataset for the descriptive analyses and chi square tests, and the imputed datasets for the regression analyses.

All descriptive statistical analyses were performed using SPSS version 25.0 (IBM Corp, 2017). Chi square tests, multiple imputation, propensity score matching and logistic regression were conducted using R (R Core

Table 1 Recommendations in guidelines on cardiovascular disease prevention by the European Society of Cardiology in 2012 [6]

Medication prescription
Acetylsalicylic acid
Lipid-lowering drugs
Statins
Antihypertensive drugs (if hypertension)
ACE inhibitor/ARB (first choice for diabetics)
Beta-blockers
Calcium channel blockers
Diuretics
Treatment goals
Blood pressure
< 140/90 mmHg (< 140/80 mmHg if diabetic)
LDL-cholesterol
< 1.8 mmol/l (< 70 mg/dL)
HbA1c (if diabetic)
< 7%

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein

Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Ethics

The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics of North Norway. All participants in the Tromsø Study have given written informed consent for their data to be used in research.

Results

The basic characteristics of the study population and across the three CHD disease groups are shown in Table 2.

Use of medications for CHD was highest among participants with previous MI and lowest among those with AP only, see Fig. 2. Of those with hypertension (n = 827), 92% used antihypertensive drugs. Among users of antihypertensive drugs, the drug classes included beta-blockers (63%), ACE-inhibitors or ARBs (49%), CCBs (22%), thiazides (16%), other (17%) and unknown (9%) antihypertensive drugs (for ATC-classification of medication

Table 2 Characteristics of the study population

	Total CHD population (n = 1483)		MI (n = 753)		PCI and/or CABG, but no MI (n = 604)		AP, but no MI, PCI or CABG (n = 126)	
Sex, n (%)								
Women	446	(30.1)	174	(23.1)	203	(33.6)	69	(54.8)
Age, mean (sd)	68.7	(10.8)	69.2	(10.1)	69.2	(10.6)	63.0	(13.7)
Smoking, n (%)								
Daily smoking	182	(12.3)	96	(12.7)	67	(11.1)	19	(15.1)
Smoked previously	860	(58.0)	472	(62.7)	334	(55.3)	54	(42.9)
Self-reported health, n (%)								
Excellent/good	705	(47.5)	343	(45.6)	311	(51.5)	51	(40.5)
Neither good nor bad	602	(40.6)	318	(42.2)	232	(38.4)	52	(41.3)
Bad/very bad	153	(10.3)	79	(10.5)	53	(8.8)	21	(16.7)
Comorbidities*, n (%)								
Hypertension	827	(55.8)	433	(57.5)	328	(54.3)	66	(52.4)
Heart failure	231	(15.6)	126	(16.7)	94	(15.6)	11	(8.7)
Atrial fibrillation	283	(19.1)	138	(18.3)	111	(18.4)	34	(27.0)
Stroke	123	(8.3)	65	(8.6)	49	(8.1)	9	(7.1)
Diabetes	214	(14.4)	123	(16.3)	80	(13.2)	11	(8.7)
Renal disease	114	(7.7)	68	(9.0)	35	(5.6)	11	(8.7)
Cancer	189	(12.7)	101	(13.4)	77	(12.7)	11	(8.7)
Medications, mean number of products (sd)	4.0	(2.9)	4.3	(3.0)	3.8	(2.8)	3.0	(2.9)
Clinical measurements, mean (sd)								
Systolic blood pressure, mmHg	136	(20.9)	135	(21.7)	137	(19.9)	133	(20.3)
Diastolic blood pressure, mmHg	74	(9.9)	75	(10.0)	74	(9.6)	76	(10.1)
Total cholesterol, mmol/l†	4.6	(1.1)	4.5	(1.1)	4.7	(1.1)	5.6	(1.3)
LDL-cholesterol, mmol/l†	2.9	(1.0)	2.7	(1.0)	2.9	(1.0)	3.7	(1.2)
HDL-cholesterol, mmol/l†	1.4	(0.4)	1.4	(0.4)	1.5	(0.5)	1.5	(0.4)
Triglycerides, mmol/l‡	1.6	(1.0)	1.7	(1.0)	1.5	(0.8)	1.8	(0.9)
HbA1c, %	6.1	(0.9)	6.1	(1.0)	6.0	(0.8)	5.8	(0.5)
Glucose, mmol/l§	6.0	(2.1)	6.2	(2.3)	6.0	(1.9)	5.6	(1.3)
BMI, kg/m^2	28.4	(4.5)	28.5	(4.4)	28.1	(4.4)	28.7	(5.2)

AP, angina pectoris; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; sd, standard deviation

* Self-reported relevant comorbidities for coronary heart disease, present or previous diseases. For diabetes: present disease or use of any antidiabetic drug

† To convert to mg/dL, multiply with 38.67

‡ To convert to mg/dL, multiply with 88.57

§ To convert to mg/dL, multiply with 18.02

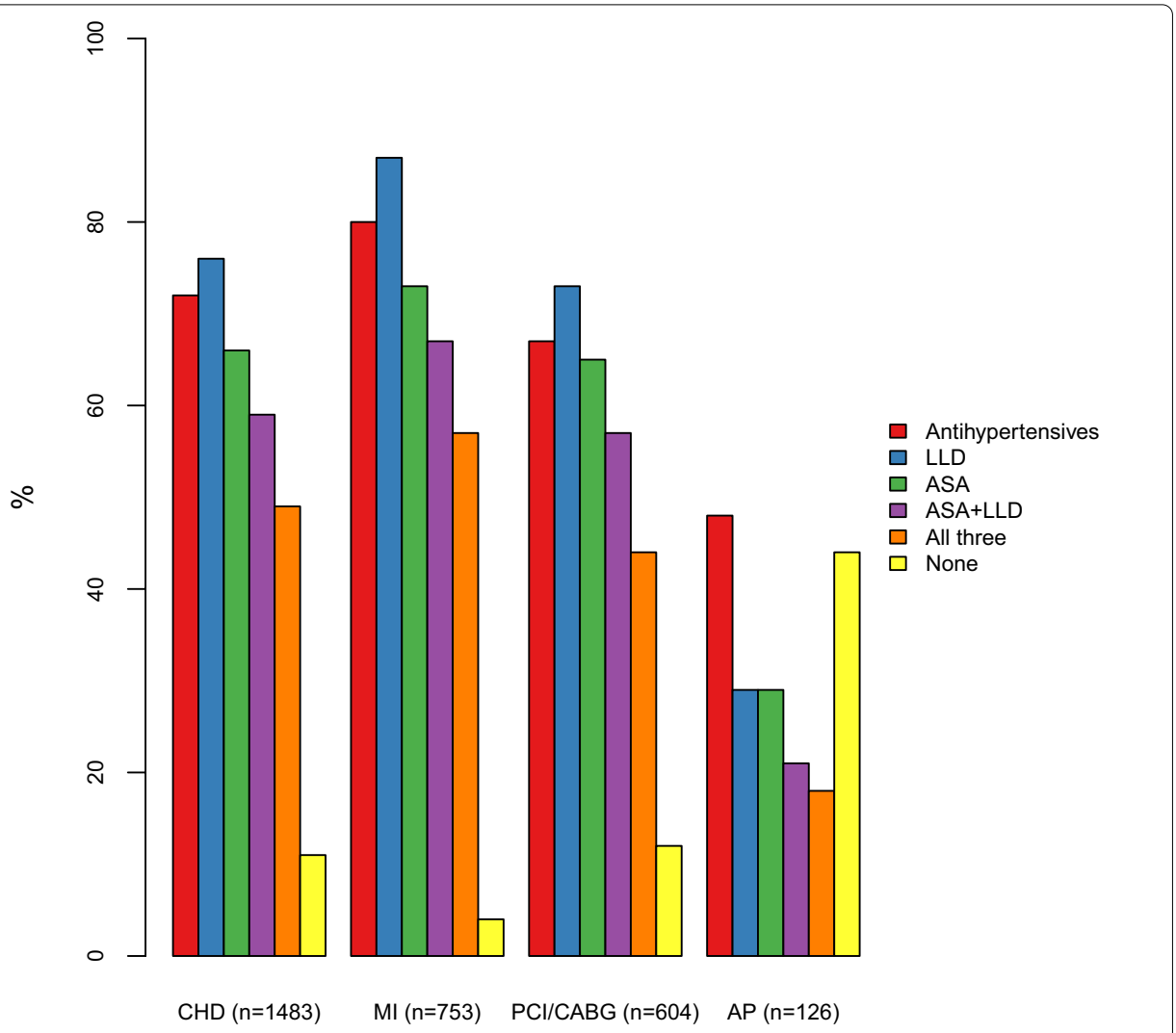

Fig. 2 Proportion of participants using medications for CHD in total and across the CHD disease groups. AP, angina pectoris; ASA, acetylsalicylic acid; CABG, coronary artery bypass surgery; CHD, coronary heart disease; LLD, lipid-lowering drug; MI, myocardial infarction; PCI, percutaneous coronary intervention

groups, see Additional file 1: Table S1). Fifty-one percent used two or more medications from different antihypertensive drug classes. The most frequent class of LLD was statins (79% of LLD users), while 20% did not report which LLD they used. As 98% of those using LLDs in Norway use statins [17], these were assumed to be statin users. Among the LLD-users, 3% used another LLD in combination with a statin, while 1% used another LLD, but not a statin.

Blood pressure goal achievement (< 140/90 mmHg, < 140/80 mmHg in persons with diabetes) was highest among those with AP only and lowest among those without MI but previous PCI or CABG, see Fig. 3a. Among those reporting having hypertension, 49% reached the treatment goal for blood pressure. For comparison, Fig. 3a also includes the proportion having a blood pressure < 150/90 mmHg.

LDL-cholesterol goal achievement (< 1.8 mmol/l or < 70 mg/dL) was highest among those with previous MI and lowest among those with AP only, see Fig. 3b. For comparison, Fig. 3b also includes the proportions having LDL-cholesterol < 2.5 mmol/L (< 97 mg/dL) and < 3.0 mmol/L (< 116 mg/dL), the recommended treatment goals for persons at high and moderate risk of CHD respectively.

Thirty-eight percent of the study population did not reach any of the two treatment goals and 6% reached both (Fig. 3c). In the study population, 5% were completely in

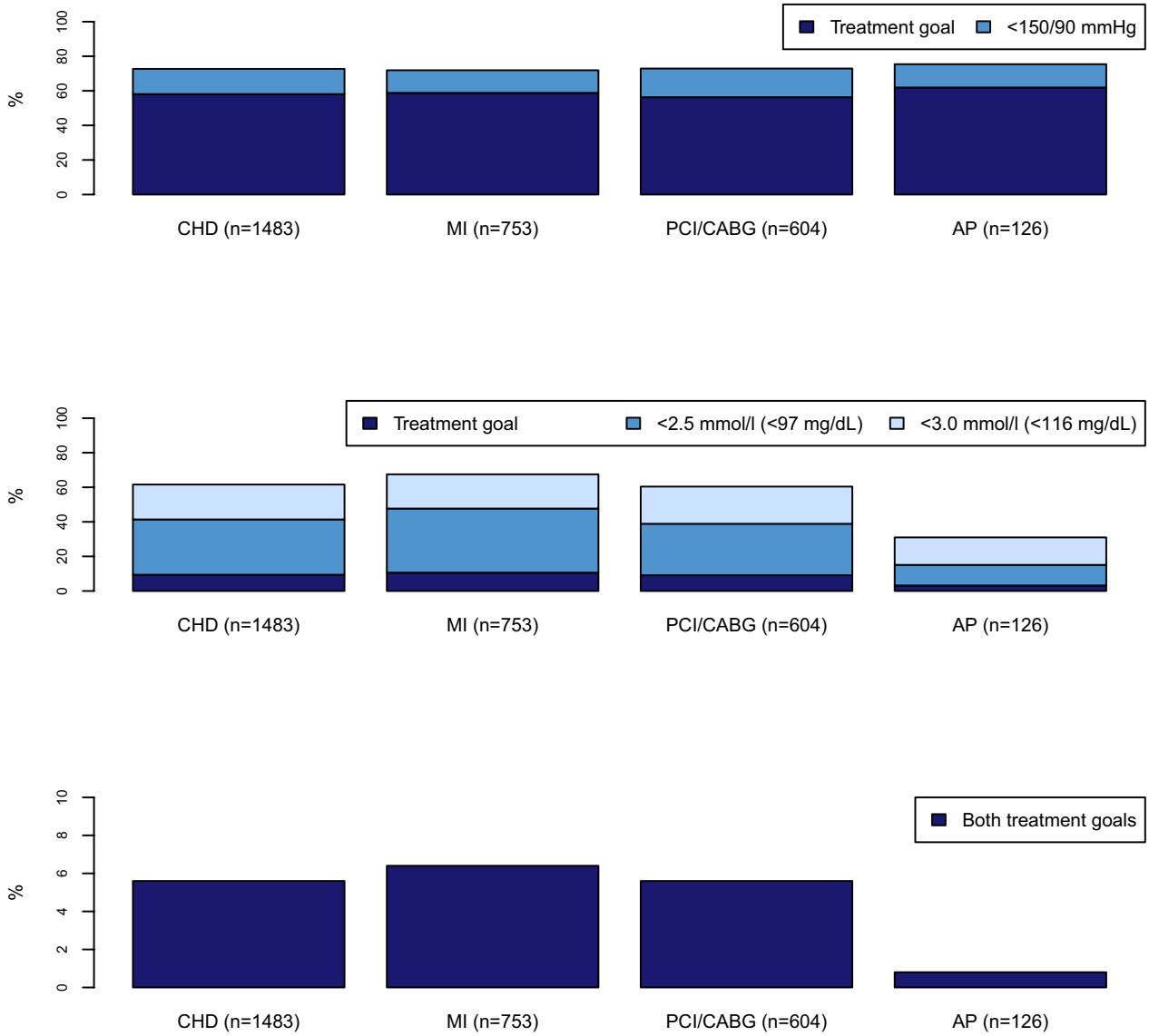

Fig. 3 Proportion of participants achieving the treatment goals, in total and across the CHD disease groups. **a** Blood pressure, treatment goal < 140/90 mmHg (< 140/80 mmHg if diabetic). The panel also shows the proportion with blood pressure close to treatment goal. **b** Low-density lipoprotein (LDL)-cholesterol, treatment goal < 1.8 mmol/l (< 70 mg/dL). The panel also shows the proportion with LDL-cholesterol < 2.5 mmol/l (< 97 mg/dL, treatment goal for persons at high risk of CHD) and < 3.0 mmol/l (< 116 mg/dL, treatment goal for persons at moderate risk of CHD). **c** both treatment goals (y-axis 0–10%). AP, angina pectoris; CABG, coronary artery bypass surgery; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention

accordance with the guidelines, i.e. using ASA and LLDs and achieving both treatment goals. The proportion reaching both treatment goals was 9% (62) among those who used all three classes of drugs and 3% (21) among those who did not use all three ($p < 0.001$). Regarding CHD disease group, the proportion reaching both treatment goals was 6% (48) among those with a previous MI, 6% (34) among those with PCI and/or CABG and 1% (1) among those with AP ($p = 0.04$). Characteristics of participants achieving and not achieving the recommended treatment goals for LDL-cholesterol and blood pressure among those using LLDs and antihypertensive drugs are shown in Table 3.

Among the participants with diabetes (n = 214), 50% achieved the treatment goal for blood pressure (< 140/80 mmHg) and 14% for LDL-cholesterol (< 1.8 mmol/L or < 70 mg/dL). Treatment goal for HbA1c (< 7%) was reached by 43% (for results on treatment goal

Table 3 Characteristics of participants achieving and not achieving treatment goals among LLD and antihypertensive drug users

	Users of LLDs (n = 1133)				Users of antihypertensive drugs among participants with hypertension (n = 763)			
	Achieving LDL-goal (n = 136)		Not achieving LDL-goal (n = 991)		Achieving BP-goal (n = 379)		Not achieving BP-goal (n = 382)	
Sex, n (%)								
Women	29	(21.3)	262	(26.4)	123	(32.5)	132	(34.6)
Age, mean (sd)	69.7	(9.5)	69.4	(9.8)	68.0	(9.7)	71.6	(9.6)
Smoking, n (%)								
Daily smoking	15	(11.0)	114	(11.5)	52	(13.7)	29	(7.5)
Smoked previously	79	(58.1)	617	(62.3)	218	(57.5)	236	(61.8)
Self-reported health, n (%)								
Excellent/good	56	(41.2)	478	(48.2)	157	(41.4)	161	(42.1)
Neither good nor bad	68	(50.0)	403	(40.7)	175	(46.2)	177	(46.3)
Bad/very bad	9	(6.6)	99	(10.0)	44	(11.6)	40	(10.4)
Comorbidities*, n (%)								
Heart failure	20	(14.7)	176	(17.8)	72	(19.0)	65	(17.0)
Atrial fibrillation	23	(16.9)	181	(18.3)	84	(22.1)	76	(19.9)
Stroke	12	(8.8)	90	(9.1)	45	(11.9)	46	(12.0)
Diabetes	28	(20.6)	147	(14.8)	72	(19.0)	74	(19.4)
Renal disease	7	(5.2)	71	(7.1)	25	(6.6)	40	(10.5)
Cancer	18	(13.2)	124	(12.5)	44	(11.6)	60	(15.8)
Medications, mean number of products (sd)	5.3	(2.9)	4.4	(2.8)	5.0	(2.9)	5.0	(2.9)
Clinical measurements, mean (sd)								
Systolic blood pressure, mmHg	133	(18.5)	136	(21.0)	123	(11.7)	155	(15.4)
Diastolic blood pressure, mmHg	73	(9.2)	74	(9.8)	71	(8.5)	79	(9.6)
Total cholesterol, mmol/l†	3.3	(0.6)	4.5	(0.9)	4.4	(1.0)	4.6	(1.1)
LDL-cholesterol, mmol/l†	1.5	(0.2)	2.7	(0.8)	2.7	(0.9)	2.8	(1.0)
HDL-cholesterol, mmol/l†	1.5	(0.6)	1.4	(0.4)	1.4	(0.4)	1.4	(0.4)
Triglycerides, mmol/l‡	1.5	(1.6)	1.6	(0.9)	1.7	(0.9)	1.7	(1.1)
HbA1c, %	6.3	(1.0)	6.1	(0.9)	6.1	(1.0)	6.1	(1.0)
Glucose, mmol/l§	6.5	(2.7)	6.0	(2.1)	6.2	(2.3)	6.2	(2.2)
BMI, kg/m^2	28.4	(4.6)	28.4	(4.3)	29.2	(4.6)	28.9	(4.4)

Percentages are calculated for columns

AP, angina pectoris; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLD, lipid-lowering drugs; MI, myocardial infarction; PCI, percutaneous coronary intervention; sd, standard deviation

* Self-reported relevant comorbidities for coronary heart disease, present or previous diseases

† To convert to mg/dL, multiply with 38.67

‡ To convert to mg/dL, multiply with 88.57

§ To convert to mg/dL, multiply with 18.02

achievement for HbA1c in the different CHD disease groups, see Additional file 1: Table S4). All three treatment goals were reached by 4%.

Logistic regression with propensity score matching showed that use of LLDs was significantly associated with treatment goal achievement for LDL-cholesterol, while the use of antihypertensive drugs among participants with hypertension was not associated with treatment goal achievement for blood pressure, see Table 4. Results from the propensity score matching can be found in Additional file 1: Tables S5 and S6.

Discussion

We have identified that a relatively high proportion of persons with CHD adhere to the recommended prescription guidelines. However, fewer of the participants in our study use LLDs, antihypertensive drugs and ASA compared to what has been found in other studies [7, 8, 18,

Table 4 Pooled results from the logistic regression analyses of the propensity score matched multiple imputed datasets

Exposure variable	Outcome variable	Odds ratio	95% confidence interval
Use of lipid-lowering drugs	Achievement of treatment goal for LDL-cholesterol	14.0	3.6–54.7
Use of antihypertensive drugs	Achievement of treatment goal for blood pressure	1.3	0.7–2.6

Number of cases varied between datasets and can be found in Additional file 1: Tables S5 and S6

19]. The newest EUROASPIRE survey from 2019 found a proportion of use of 84% for LLDs, 95% for antihypertensive drugs and 93% for antiplatelet drugs [7]. The results from The NORwegian CORonary (NOR-COR) Prevention Study, STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) study and the prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) study are also similar to that of the EUROASPIRE [8, 18, 19]. Unlike our study, most of these studies attain their information about medication use from medical journals and the studies are usually conducted within a limited time frame after discharge from the hospital. As far as we know, ours is the first study to focus on persons with CHD in a general population, independent of time since diagnosis, and to investigate the participants' own self-reported use of medications.

Compared with other studies, the use of ASA and other antiplatelet drugs in our study is especially low [7, 8, 18, 19]. The guidelines recommend use of ASA as secondary prevention for those who have had an MI, PCI or CABG, i.e., not including persons with only AP. In the current study, 70% within this subpopulation (n = 1357) used ASA, which is lower than what has been reported previously [7, 8]. Including other antiplatelet drugs increased the proportion of users to 71%, while the proportion of users of any antithrombotic drug (antiplatelets or anticoagulants) was 78%. Although there will always be some who cannot use antithrombotics, this user prevalence is lower than expected.

Despite high prevalence of use of antihypertensive drugs and LLDs, achievement of treatment goals was low, especially for LDL-cholesterol. This is also comparable to what has been found in other studies, though the level of achievement for LDL-cholesterol was lower in our study [7, 8, 20, 21]. Since our study population is defined as participants already having heart disease, they are considered to have a very high cardiovascular (CVD) risk, and the guidelines therefore recommend a treatment goal for LDL-cholesterol at < 1.8 mmol/L (< 70 mg/dL) or a reduction of ≥ 50% for LDL-cholesterol when the target cannot be reached [6]. As this is a cross-sectional study, we do not know the participants' cholesterol levels at treatment initiation and are therefore not able to determine whether they have had a 50% reduction in LDL-cholesterol. However, even when applying a threshold of < 3 mmol/L (< 116 mg/dL), only 62% achieve the treatment goal (Fig. 3b). This indicates that many participants were far from reaching the recommended treatment goal.

The proportion of participants using antihypertensive drugs and achieving the treatment goals for blood pressure was comparable to what has been found in other studies [7–9, 18, 19]. These studies do not however explore the relationship between the two. We did not find a statistically significant relationship between using antihypertensive drugs and achieving the treatment goal for blood pressure. One plausible explanation for this is that participants who had been prescribed antihypertensive drugs probably had a higher baseline blood pressure than those who were not prescribed antihypertensive drugs. If so, some of the participants using antihypertensive drugs may have experienced a reduction in blood pressure, though not enough to reach the recommended treatment goal. Non-adherence could also be a potential explanation why we do not detect a statistically significant difference in achievement of treatment goal between participants using and not using antihypertensive drugs. Another possibility is that our population is too small, as so few persons with hypertension were not using antihypertensive drugs. This affects the propensity score matching, and makes it difficult to achieve comparable groups that are similar enough on all variables used in the propensity score. Further studies using a larger hypertensive population is therefore needed to confirm these results.

Of the three CHD disease groups, persons with previous MI, PCI or CABG have a higher risk of new major coronary events and require a closer follow-up than persons with only self-reported AP. We found that among participants within the PCI or CABG group, fewer persons reached the treatment goals for both blood pressure and LDL-cholesterol and fewer of these persons used LLDs, antihypertensive drugs and ASA compared to those with previous MI (Figs. 2 and 3). This suggests that these persons need closer follow-up.

Strengths and limitations

We have used data from the Tromsø Study, a reliable population-based data source where measurements

of blood pressure and cholesterol were performed by trained personnel and with standardized procedures and instruments. The Tromsø Study has a high attendance rate and is considered representative for an urban, white Northern European population [15].

Measurements of blood pressure and LDL-cholesterol were done objectively, which is also a strength of the study. So is the use of multiple imputation to avoid bias due to missing values and propensity score matching to control for confounding. Propensity score matching appropriately balances the covariates between treated and untreated participants and makes it possible to include more covariates than in a conventional multivariable logistic regression.

The major limitation in this study is that we do not have any information about blood pressure and LDL-cholesterol at treatment initiation, which restricts us to investigating the participants' blood pressure and LDL-cholesterol at the time of their attendance in Tromsø 7.

We also lack information about the participants' medication adherence; hence we do not know if the participants actually take their medication as prescribed. Non-adherence is likely to reduce their achievement of treatment goals.

Another limitation of the study is that most variables are self-reported, including CHD diagnosis and use of medications. We may have underestimated adherence to treatment guidelines through inclusion of some participants that are not actual CHD patients, or exclusion of participants who did not recall a previous CHD event. Such misclassification is less likely for life threatening conditions like MI, and although there may be some who reported MI when they have had a PCI/CABG (or vice versa), the extent would be limited and should not noteworthy alter the study results. Self-reported medication use could make the results susceptible to recall bias. For medications used for chronic conditions such as CHD, self-reported use of medications have shown good to very good agreement with prescription data [22], suggesting that recall bias should be a minor problem in our study.

A disadvantage with the statistical methods is that propensity score matching does not use all the observations. This is especially a problem when the groups of treated and untreated are very unevenly distributed, as in our study population (76% use LLDs and 92% of those with hypertension use antihypertensive drugs). To include as many observations as possible we performed matching with replacement. This procedure may introduce bias as several participants among medication users can be matched with the same non-user, and some may not be matched to anyone at all. However, a re-analysis without replacement gave very similar result, suggesting our results are valid (for results from this sensitivity analysis, see Additional file 1: Table S7). As propensity score matching only controls for measured confounders, our results might still be affected by unmeasured variables, which are only controllable through randomization.

Conclusion

Despite high adherence to prescription guidelines and a strong association between use of LLDs and treatment goal achievement, the proportion who reaches the treatment goals is low among persons with CHD in a general population. Further research should include longitudinal studies to explore dosage regimens and medication adherence among persons with CHD over time.

Abbreviations

ACE: Angiotensin converting enzyme; AP: Angina pectoris; ARB: Angiotensin receptor blocker; ASA: Acetylsalicylic acid; ATC: Anatomical therapeutic chemical; BMI: Body mass index; CABG: Coronary artery bypass surgery; CCB: Calcium channel blocker; CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; EUROASPIRE: European survey of cardiovascular disease prevention and diabetes; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LLD: Lipid-lowering drug; MI: Myocardial infarction; OR: Odds ratio; PCI: Percutaneous coronary intervention; SD: Standard deviation; SPSS: Statistical Package for the Social Sciences.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-021-01866-1.

Additional file 1: Table S1. Overview of ATC-codes included in the three medication categories recommended for CHD based on the European Society of Cardiology: Guidelines on cardiovascular disease prevention in clinical practice (version 2012) [6]. **Table S2.** Variables included as covariates in propensity score. **Table S3.** Variables included in multiple imputation. **Table S4.** Achievement of treatment goal for HbA1c for participants with diabetes in the different CHD disease groups. **Table S5.** Results from propensity score matching of the ten imputed datasets for the logistic regression analysis of the association between use of lipid-lowering drugs and achieving the treatment goal for LDL-cholesterol. **Table S6.** Results from propensity score matching of the ten imputed datasets for the logistic regression analysis of the association between use of antihypertensive drugs and achieving the treatment goal for blood pressure among those with self-reported hypertension. **Table S7.** Pooled results from the sensitivity analysis for the logistic regression analyses of the multiple imputed datasets, using propensity score matching without replacement.

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Authors' contributions

EP, MW, BHG, KHH, AEE and HS contributed to the conception and/or design of the work. EP, AEE and HS contributed to the acquisition of data for the work. EP drafted the manuscript and conducted the analyses. All contributed to the interpretation of data and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Availability of data and materials
The owner of the data is the Tromsø Study. We have permission to analyse the data according to the protocol submitted to the Tromsø Study; however, we do not have permission to share the data. Other interested researchers can request the data in the same manner if they comply with the requirements of the institution (https://en.uit.no/forskning/forskningsgrupper/sub?p_document_id=453582&sub_id=66 9706).

Ethics approval and consent to participate
The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics of North Norway (approval reference 2014/940 for Tromsø 7 and 2015/1775 for the current study). All participants in the Tromsø Study have given written informed consent for their data to be used in research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

BMC Cardiovascular Disorders

CORRECTION

Open Access

Correction to: Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7

Elisabeth Pedersen[1*], Beate Hennie Garcia[1], Kjell H. Halvorsen[1], Anne Elise Eggen[2], Henrik Schirmer[3,4] and Marit Waaseth[1]

Correction to: BMC Cardiovasc Disord (2021) 21:44
https://doi.org/10.1186/s12872-021-01866-1

Following publication of the original article [1], the authors would like to correct some information in the fourth paragraph under 'Data extraction' in the methods section. We have found that the LDL-cholesterol concentrations included in the study were measured directly, not calculated from total cholesterol.

The information originally read:

Serum total cholesterol was analysed by CHOD-PAP enzymatic colorimetric methods with commercial kits (Roche Diagnostics GmbH, Mannheim, Germany) from non-fasting blood samples. The analysis was performed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway. LDL-cholesterol concentration was then calculated according to Friedewald's formula: LDL-cholesterol = total cholesterol − high-density lipoprotein cholesterol − (0.45 × triglycerides).

The information should read:

LDL-cholesterol was collected and analyzed by trained personnel using enzymatic colorimetric methods with commercial kits on a Cobas 8000 c702 (Roche Diagnostics GmbH, Mannheim, Germany) from non-fasting venous blood samples. The analysis was performed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway (ISO certification NS-EN ISO 15189:2012).

The original article [1] has been corrected.

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Supplementary material

Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7

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Content:

Supplementary table 1: Overview of ATC-codes included in the three medication categories recommended for CHD based on the European Society of Cardiology: Guidelines on cardiovascular disease prevention in clinical practice (version 2012) (6)

Medication	ATC-codes
Acetylsalicylic acid[1]	
Acetylsalicylic acid	B01AC06
Lipid lowering drugs	
Statins	C10AA, C10BA
Other lipid lowering drugs	C10AC, C10AX
Unknown lipid lowering drugs[2]	
Antihypertensive drugs	
ACE inhibitors and ARBs	C09
Beta-blockers	C07
Calcium channel blockers	C08, C09BB, C09DB, C09DX01, C09DX03
Thiazides	C03A, C03EA, C07B, C09BA, C09DA, C09DX01, C09DX03
Other antihypertensives[2]	C02, C03C, C03D, C03EA, C03X
Unknown antihypertensives[2]	

[1] Also includes "yes" to question "If you have used analgesics and anti-inflammatory medication regularly in the past year - did you use "Baby" or low dose acetylsalicylic acid (ASA) Acetylsalisylsyre® Albyl-E® Asasantin Retard® (75/160 mg per tablet)?"

[2] When, instead of brand name, the participants in free text reported using medication interpretable as "blood pressure lowering", "diuretics" or "cholesterol lowering", it was registered under the respective medication category.

Supplementary table 2: Variables included as covariates in propensity score

Variable name	Variable explanation	Coding
AGE	Number of years at attendance date	Number
SEX_T7	Sex	1 : Male 0 : Female
BMI	Body mass index	Number
HEART_FAILURE_T7	Have you ever had, or do you have heart failure?	0 : No 1 : Yes, now 2 : Yes, previously
ATRIAL_FIBRILLATION_T7	Have you ever had, or do you have atrial fibrillation?	0 : No 1 : Yes, now 2 : Yes, previously
STROKE_T7	Do you have, or have you had a cerebral stroke/brain haemorrhage?	0 : No 2 : Yes, previously
KIDNEY_DISEASE_T7	Do you have, or have you had a kidney disease, not including urinary tract infection (UTI)?	0 : No 1 : Yes, now 2 : Yes, previously
CANCER_T7	Have you ever had, or do you have cancer?	0 : No 1 : Yes, now 2 : Yes, previously
DIABETES_impu_new[1]	Do you have, or have you had diabetes?	0 : No 1 : Yes, now 2 : Yes, previously
Cons_GP_Times_impu[1]	If you have visited a general practitioner (GP) the past year, how many visits have you made?	Number
Cons_Emergency_Times_impu[1]	If you have visited an emergency room the past year, how many visits have you made?	Number
Cons_Hospital_Times_impu[1]	If you have been admitted to a hospital the past year, how many times?	Number
Cons_Specialist_Times_impu[1]	If you have visited another medical specialist than a general practitioner (GP) or a psychologist or psychiatrist (not at a hospital) the past year, how many visits have you made?	Number
Cons_Clinic_Times_impu[1]	Have you during the past year visited a hospital out-patient clinic, other than psychiatric department?	Number
Alcohol_frequency_impu[1]	How often do you usually drink alcohol?	1 : Never 2 : Monthly or less frequently 3 : 2-4 times a month 4 : 2-3 times a week 5 : 4 or more times a week
Alcohol_units_impu[1]	How many units of alcohol (1 beer, glass of wine or drink) do you usually drink when you drink alcohol?	1 : 1-2 2 : 3-4 3 : 5-6 4 : 7-9 5 : 10 or more
Alcohol_units_6_impu[1]	How often do you drink 6 units alcohol or more in one occasion?	1 : Never 2 : Less frequently than monthly

		3 : Monthly 4 : Weekly 5 : Daily or almost daily
Smoke_impu[1]	Do you/did you smoke daily/sometimes?	1 : Now, daily 2 : Now, sometimes 3 : Previously 4 : Never
Snuff_chewing_tobacco_impu[1]	Have you used or do you use snuff or chewing tobacco daily/sometimes?	1 : Now, daily 2 : Now, sometimes 3 : Previously 4 : Never
Cod_liver_oil_omega3_impu[1]	Do you use cod liver oil or cod liver oil capsules or Omega 3 capsules (fish oil, seal oil)?	0 : No 1 : Sometimes 2 : Daily during the winter season 3 : Daily
FRUIT_UNITS_T7	How many units of fruit or vegetables do you eat per day (average). (E.g. an apple, bowl of salad)?	Number
RED_MEAT_T7	How often do you usually eat red meat (all products from beef, mutton, pork)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more
FRUITS_VEG_BERRY_T7	How often do you usually eat fruits, vegetables and berries?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more
LEAN_FISH_T7	How often do you usually eat lean fish (cod, saithe)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more
FAT_FISH_T7	How often do you usually eat fat fish (salmon, trout, redfish, mackerel, herring, halibut)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more
PHYS_ACTIVITY_LEISURE_T7	Describe your exercise and physical exertion in leisure time over the last year. If your activity varies throughout the year, give an average.	1 : Reading, watching TV/screen or other sedentary activity? 2 : Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.) 3 : Participation in recreational sports, heavy gardening, snow shoveling etc at least 4 hours a week. 4 : Participation in hard training or sports competitions, regularly several times a week?
EXERCISE_T7	How often do you exercise (i.e walking, skiing, swimming or training/sports)?	1 : Never 2 : Less than once a week 3 : Once a week 4 : 2-3 times a week

[1] Combination of several variables from Tromsø 7

Supplementary table 3: Variables included in multiple imputation

Variable name	Variable explanation	Coding	Missing before imputation in CHD population (n=1483), n (%)	Missing before imputation in hypertensive CHD population (n=827), n (%)
SEX_T7	Sex	1 : Male 0 : Female	0 (0.0)	0 (0.0)
TIME_LAST_MEAL_T7	Time since last meal	0 : < 1 hour 1 : 1-1.59 hours 2 : 2-2.59 hours 3 : 3-3.59 hours 4 : 4-4.59 hours 5 : 5-5.59 hours 6 : 6-6.59 hours 7 : 7-7.59 hours 8 : 8-8.59 hours 9 : 9+ hours	2 (0.1)	1 (0.1)
S_LDL_T7[1]	Serum low density lipoprotein cholesterol (mmol/l)	Number	11 (0.7)	6 (0.7)
S_HDL_T7[1]	Serum High density lipoprotein cholesterol (mmol/l)	Number	11 (0.7)	6 (0.7)
S_CHOLESTEROL_T7[1]	Serum Total cholesterol (mmol/l)	Number	11 (0.7)	6 (0.7)
S_TRIGLYCERIDES_T7	Serum Triglycerides (mmol/l)	Number	11 (0.7)	6 (0.7)
S_GLUCOSE_T7	Serum glucose (mmol/l)	Number	9 (0.6)	4 (0.5)
S_CREATININ_T7	Serum creatinin (µmol/L)	Number	9 (0.6)	4 (0.5)
B_HBA1C_T7	HBA1C (%)	Number	22 (1.5)	11 (1.3)
HEALTH_T7	How do you in general consider your own health to be?	5 : Excellent 4 : Good 3 : Neither good nor bad 2 : Bad 1 : Very bad	23 (1.6)	7 (0.8)
HEALTH_COMPARED_T7	How is your health now compared to others of your age?	5 : Much better 4 : A little better 3 : About the same 2 : A little worse 1 : Much worse	34 (2.3)	16 (1.9)

HIGH_BLOOD_PRESSURE_T7	Have you ever had, or do you have high blood pressure?	0 : 1 : 2 :	No Yes, now Yes, previously	76	(5.1)	0 (0.0)
HEART_ATTACK_T7	Do you have, or have you had a heart attack?	0 : 2 :	No Yes, previously	97	(6.5)	48 (5.8)
HEART_FAILURE_T7	Have you ever had, or do you have heart failure?	0 : 1 : 2 :	No Yes, now Yes, previously	182	(12.3)	95 (11.5)
ATRIAL_FIBRILLATION_T7	Have you ever had, or do you have atrial fibrillation?	0 : 1 : 2 :	No Yes, now Yes, previously	157	(10.6)	82 (9.9)
ANGINA_T7	Do you have, or have you had angina pectoris (heart cramp)?	0 : 1 : 2 :	No Yes, now Yes, previously	130	(8.8)	66 (8.0)
STROKE_T7	Do you have, or have you had a cerebral stroke/brain haemorrhage?	0 : 2 :	No Yes, previously	112	(7.6)	50 (6.0)
KIDNEY_DISEASE_T7	Do you have, or have you had a kidney disease, not including urinary tract infection (UTI)?	0 : 1 : 2 :	No Yes, now Yes, previously	122	(8.2)	59 (7.1)
BRONCHITIS_T7	Have you ever had, or do you have chronic bronchitis/emphysema/COPD?	0 : 1 : 2 :	No Yes, now Yes, previously	106	(7.1)	54 (6.5)
ASTHMA_T7	Do you have, or have you had asthma?	0 : 1 : 2 :	No Yes, now Yes, previously	98	(6.6)	49 (5.9)
CANCER_T7	Have you ever had, or do you have cancer?	0 : 1 : 2 :	No Yes, now Yes, previously	94	(6.3)	45 (5.4)
RHEUMATOID_ARTHRITIS_T7	Have you ever had, or do you have rheumatoid arthritis?	0 : 1 : 2 :	No Yes, now Yes, previously	125	(8.4)	68 (8.2)
ARTHROSIS_T7	Have you ever had, or do you have arthrosis?	0 : 1 : 2 :	No Yes, now Yes, previously	124	(8.4)	61 (7.4)
MIGRAINE_T7	Have you ever had, or do you still have migraine?	0 : 1 : 2 :	No Yes, now Yes, previously	103	(6.9)	55 (6.7)

PSYCHOLOGICAL_PROBLEMS_T7	Have you ever had, or do you have psychological problems for which you have sought help?	0 : 1 : 2 :	No Yes, now Yes, previously	115	(7.8)	57	(6.9)
CHRONIC_PAIN_T7	Do you have persistent or constantly recurring pain that has lasted for 3 months or more?	0 : 1 :	No Yes	282	(19.0)	157	(19.0)
CONSULTATION_PSYC_T7	Have you during the past year visited a psychologist or psychiatrist?	0 : 1 :	No Yes	105	(7.1)	45	(5.4)
CONSULTATION_DENTIST_T7	Have you during the past year visited a dentist/dental service?	0 : 1 :	No Yes	49	(3.3)	20	(2.4)
CONSULTATION_PHARMACY_T7	Have you during the past year visited a pharmacy (to buy/get advice about medicines/treatment)?	0 : 1 :	No Yes	87	(5.9)	38	(4.6)
CONS_PHYSIOTHERAPIST_T7	Have you during the past year visited a physiotherapist?	0 : 1 :	No Yes	82	(5.5)	36	(4.4)
CONSULTATION_CHIROPRACTOR_T7	Have you during the past year visited a chiropractor?	0 : 1 :	No Yes	89	(6.0)	39	(4.7)
COMM_HEALTH_INTERNET_T7	Have you during the past year communicated with any of the services above by using the Internet?	0 : 1 :	No Yes	86	(5.8)	37	(4.5)
CONSULTATION_HOSPITAL_PSYC_T7	Have you during the past year visited a hospital out-patient clinic, psychiatric department?	0 : 1 :	No Yes	193	(13.0)	97	(11.7)
BP_TREATMENT_T7	Do you use, or have you used blood pressure lowering drugs?	1 : 2 : 3 :	Currently Previously, not now Never used	72	(4.9)	11	(1.3)
DIURETICS_T7	Do you use, or have you used diuretics?	1 : 2 : 3 :	Currently Previously, not now Never used	145	(9.8)	78	(9.4)
HEART_DISEASE_MEDICINE_T7	Do you use, or have you used drugs for heart disease (for example anticoagulants, antiarrhythmics, nitroglycerin)?	1 : 2 : 3 :	Currently Previously, not now Never used	86	(5.8)	37	(4.5)
INSULIN_T7	Do you use, or have you used insulin?	1 : 2 :	Currently Previously, not now	142	(9.6)	68	(8.2)

		3 : Never used		
DIABETES_TABLETS_T7	Do you use, or have you used tablets for diabetes?	1 : Currently 2 : Previously, not now 3 : Never used	111 (7.5)	57 (6.9)
THYROXINE_T7	Do you use, or have you used drugs for hypothyroidism (Levaxin or thyroxine)?	1 : Currently 2 : Previously, not now 3 : Never used	122 (8.2)	62 (7.5)
PAINKILLERS_PRESC_4WEEKS_T7	How often have you used painkillers with prescription during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	103 (6.9)	54 (6.5)
PAINKILLERS_NOPRESC_4WEEKS_T7	How often have you used painkillers without prescription during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	100 (6.7)	54 (6.5)
ACID_SUPRESSIVES_4WEEKS_T7	How often have you used acid suppressive medication during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	121 (8.2)	62 (7.5)
SLEEPING_PILLS_4WEEKS_T7	How often have you used sleeping pills during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	112 (7.6)	56 (6.8)
TRANQUILIZERS_4WEEKS_T7	How often have you used tranquilizers during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	140 (9.4)	74 (8.9)

ANTIDEPRESSANTS_4WEEKS_T7	How often have you used antidepressants during the last 4 weeks?	1 : Not used 2 : Less frequently than every week 3 : Every week, but not daily 4 : Daily	161	(10.9)	91	(11.0)
FRUIT_UNITS_T7	How many units of fruit or vegetables do you eat per day (average). (E.g. an apple, bowl of salad)?	Number	76	(5.1)	41	(5.0)
RED_MEAT_T7	How often do you usually eat red meat (all products from beef, mutton, pork)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more	42	(2.8)	20	(2.4)
FRUITS_VEG_BERRY_T7	How often do you usually eat fruits, vegetables and berries?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more	31	(2.1)	13	(1.6)
LEAN_FISH_T7	How often do you usually eat lean fish (cod, saithe)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more	32	(2.2)	17	(2.1)
FAT_FISH_T7	How often do you usually eat fat fish (salmon, trout, redfish, mackerel, herring, halibut)?	1 : 0-1 times per month 2 : 2-3 times per month 3 : 1-3 times per week 4 : 4-6 times per week 5 : Once a day or more	37	(2.5)	18	(2.2)
PHYS_ACTIVITY_LEISURE_T7	Describe your exercise and physical exertion in leisure time over the last year. If your activity varies throughout the year, give an average.	1 : Reading, watching TV/screen or other sedentary activity? 2 : Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.)	112	(7.6)	54	(6.5)

		3 : Participation in recreational sports, heavy gardening, snow shoveling etc at least 4 hours a week. 4 : Participation in hard training or sports competitions, regularly several times a week?				
HOURS_SITTING_WEEKDAY_T7	During the last week, how much time did you spend sitting on a typical weekday? E.g. at at desk, while visiting friends, while watching TV/screen (including both work and leisure time)	Number	326	(22.0)	181	(21.9)
HOURS_SITTING_WEEKEND_T7	During the last week, how much time did you spend sitting on a typical weekend day? E.g. at a desk, while visiting friends, while watching TV/screen	Number	376	(25.4)	211	(25.5)
EDUCATION_T7	What is the highest levels of education you have completed?	1 : Primary/partly secondary education. (Up to 10 years of schooling) 2 : Upper secondary education: (a minimum of 3 years) 3 : Tertiary education, short: College/university less than 4 years 4 : Tertiary education, long: College/university 4 years or more	64	(4.3)	31	(3.7)
LIVE_WITH_SPOUSE_T7	Do you live with a spouse/partner?	0 : No 1 : Yes	105	(7.1)	53	(6.4)
LIVE_WITH_O18_T7	Do you live with persons older than 18 years of age other than your spouse/partner?	0 : No 1 : Yes	500	(33.7)	266	(32.2)
LIVE_WITH_Y18_T7	Do you live with persons younger than 18 years of age?	0 : No 1 : Yes	541	(36.5)	295	(35.7)

SUPPORT_FRIENDS_T7	Do you have enough friends who can give you help and support when you need it?	0 : No 1 : Yes	50	(3.4)	23	(2.8)
HEALTH_SCALE_T7	We would like to know how good or bad your health is today. This scale is numbered from 0-100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Please insert a number between 0 and 100 here.	Number	40	(2.7)	20	(2.4)
BIOLOGICAL_CHILD_NUMBER_T7	How many children do you have? Number of biological children.	Number	73	(4.9)	37	(4.5)
MOTHER_ALIVE_T7	Is your mother alive?	0 : No 1 : Yes	29	(2.0)	11	(1.3)
MOTHER_AGE_DEAD_T7	If your mother is dead, how old was she when she died?	Number	320	(21.6)	160	(19.3)
FATHER_ALIVE_T7	Is your father alive?	0 : No 1 : Yes	36	(2.4)	17	(2.1)
FATHER_AGE_DEAD_T7	If your father is dead, how old was he when he died?	Number	205	(13.8)	97	(11.7)
ECONOMY_T7	How would you evaluate your finances?	1 : Very good 2 : Good 3 : Average 4 : Difficult 5 : Very difficult	30	(2.0)	15	(1.8)
OCCUPATION_T7	What is your main occupation/activity?	1 : Works full time 2 : Works part time 3 : Unemployed 4 : Housekeeping 5 : Retired 6 : Student/military service 7 : Disabilty benefit recipient/work assessment allowance 8 : Family income supplement	29	(2.0)	14	(1.7)

OCCUPATION_STATUS_T7	I consider my occupation to have the following social status in the society: (if you are not currently employed, think about your latest occupation)	1 : Very high social status 2 : Fairly high social status 3 : Neither high nor low status 4 : Fairly low status 5 : Very low status	71	(4.8)	38	(4.6)
BYPASS_T7	Have you had coronary artery bypass surgery?	0 : No 1 : Yes	149	(10.0)	84	(10.2)
PCI_T7	Have you had percutaneous coronary intervention?	0 : No 1 : Yes	64	(4.3)	31	(3.7)
CLAUDICATIO_T7	Have you had claudicatio intermittens?	0 : No 1 : Yes	139	(9.4)	72	(8.7)
MEMORY_DECLINED_T7	Have your memory declined?	0 : No 1 : Yes	37	(2.5)	20	(2.4)
MEMORY_PROBLEM_DAILY_T7	If you have answered yes to one of the four first questions above (Have your memory declined? Do you often forget where you have placed your things? Do you have difficulties finding word in a casual conversation? Have you problems performing daily tasks you used to master? Have you been examined for memory problems?) Is this a problem in your daily life?	0 : No 1 : Yes	514	(34.7)	268	(32.4)
ANALGESICS_ANTIINFLAM_T7	Have you used analgesics and anti-inflammatory medication regularly in the past year? These include both over-the-counter and prescription only medicines.	0 : No 1 : Yes	37	(2.5)	22	(2.7)
REG_MEDICINES_4WEEKS_T7	Have you used medicines (non-prescription and prescription) regularly during the last 4 weeks? Do not include dietary supplements (vitamins, minerals,	0 : No 1 : Yes	43	(2.9)	25	(3.0)

	omega-3, herbs or other natural remedies)			
EXERCISE_T7	How often do you exercise (i.e walking, skiing, swimming or training/sports)?	1 : Never 2 : Less than once a week 3 : Once a week 4 : 2-3 times a week	34 (2.3)	19 (2.3)
EXERCISE_LEVEL_T7	If you exercise - how hard do you exercise?	1 : Easy - you do not become shortwinded or sweaty 2 : You become shortwinded and sweaty 3 : Hard - you become exhausted	205 (13.8)	115 (13.9)
EXERCISE_DURATION_T7	For how long time do you exercise? (give an average)	1 : Less than 15 minutes 2 : 15-29 minutes 3 : 30-60 minutes 4 : More than 1 hour	199 (13.4)	116 (14.0)
ALCOHOL_STOP_DRINKING_T7	How often during the last year have you: Not been able to stop drinking alcohol when first started?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	257 (17.3)	142 (17.2)
ALCOHOL_FAILED_EXPECTED_T7	How often during the last year have you: Failed to do what was normally expected from you because of drinking?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	263 (17.7)	145 (17.5)
ALCOHOL_MORNING_T7	How often during the last year have you: Needed alcohol in the morning to get yourself going after a heavy drinking session?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	260 (17.5)	143 (17.3)
ALCOHOL_REMORSE_T7	How often during the last year have you: Had a feeling of guilt or remorse after drinking?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	262 (17.7)	144 (17.4)

ALCOHOL_NOT_REMEMBER_T7	How often during the last year have you: Been unable to remember what happened the night before because you had been drinking?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	270	(18.2)	148	(17.9)
GET_DRUNK_FREQUENCY_T7	Approximately how often during the past 12 months have you drunk so much that you felt highly intoxicated (drunk)?	1 : Never 2 : Less than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	263	(17.7)	145	(17.5)
ALCOHOL_INJURED_T7	How often during the last year have you or someone else been injured because of your drinking?	1 : Never 2 : Yes, but not during the last year 3 : Yes, during the last year	49	(3.3)	22	(2.7)
ALCOHOL_CONCERNED_T7	How often during the last year has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?	1 : Never 2 : Yes, but not during the last year 3 : Yes, during the last year	68	(4.6)	31	(3.7)
SMOKE_START_AGE_T7	If you currently smoke, or have smoked before, how old were you when you began smoking daily?	Number	498	(33.6)	295	(35.7)
SMOKE_YEARS_T7	If you currently smoke, or have smoked before, how many years in all have you smoked daily?	Number	514	(34.7)	304	(36.8)
SMOKE_STOP_TIME_T7	If you previously smoked daily, how long is it since you stopped (years)?	Number	692	(46.7)	383	(46.3)
AGE	Number of years at attendance date	Number	0	(0.0)	0	(0.0)
SYSBP_mean[2,3]	Mean systolic blood pressure	Number	5	(0.3)	3	(0.4)
DIABP_mean[2,3]	Mean diastolic blood pressure	Number	5	(0.3)	3	(0.4)
BP_med[1]	Use of antihypertensive drugs	0 : No 1 : Yes	0	(0.0)	0	(0.0)
Chol_med[2]	Use of lipid lowering drugs	0 : No 1 : Yes	0	(0.0)	0	(0.0)

CHD_BP_treatmentgoal[1]	Mean blood pressure <140/90 mmHg	0 : No 1 : Yes	5	(0.3)	3	(0.4)
CHD_LDL_treatmentgoal[2]	LDL-cholesterol <1.8 mmol/l	0 : No 1 : Yes	11	(0.7)	6	(0.7)
BMI	Body mass index	Number	8	(0.5)	2	(0.2)
Smoke_impu[3]	Do you/did you smoke daily/sometimes?	1 : Now, daily 2 : Now, sometimes 3 : Previously 4 : Never	0	(0.0)	0	(0.0)
Snuff_chewing_tobacco_impu[3]	Have you used or do you use snuff or chewing tobacco daily/sometimes?	1 : Now, daily 2 : Now, sometimes 3 : Previously 4 : Never	3	(0.2)	2	(0.2)
Cod_liver_oil_omega3_impu[3]	Do you use cod liver oil or cod liver oil capsules or Omega 3 capsules (fish oil, seal oil)?	0 : No 1 : Sometimes 2 : Daily during the winter season 3 : Daily	38	(2.6)	21	(2.5)
Alcohol_frequency_impu[3]	How often do you usually drink alcohol?	1 : Never 2 : Monthly or less frequently 3 : 2-4 times a month 4 : 2-3 times a week 5 : 4 or more times a week	1	(0.1)	1	(0.1)
Alcohol_units_impu[3]	How many units of alcohol (1 beer, glass of wine or drink) do you usually drink when you drink alcohol?	1 : 1-2 2 : 3-4 3 : 5-6 4 : 7-9 5 : 10 or more	6	(0.4)	5	(0.6)
Alcohol_units_6_impu[3]	How often do you drink 6 units alcohol or more in one occasion?	1 : Never 2 : Less frequently than monthly 3 : Monthly 4 : Weekly 5 : Daily or almost daily	20	(1.3)	8	(1.0)
Number_X_medicines	Number of medicines listed when asked to write down the	Number	0	(0.0)	0	(0.0)

	medicines used regularly the last 4 weeks					
Cons_GP_Times_impu[3]	If you have visited a general practitioner (GP) the past year, how many visits have you made?	Number	188	(12.7)	96	(11.6)
Cons_Emergency_Times_impu[3]	If you have visited an emergency room the past year, how many visits have you made?	Number	123	(8.3)	58	(7.0)
Cons_Hospital_Times_impu[3]	If you have been admitted to a hospital the past year, how many times?	Number	64	(4.3)	29	(3.5)
Cons_Spesialist_Times_impu[3]	If you have visited another medical specialist than a general practitioner (GP) or a psychologist or psychiatrist (not at a hospital) the past year, how many visits have you made?	Number	148	(10.0)	69	(8.3)
Cons_Clinic_Times_impu[3]	Have you during the past year visited a hospital out-patient clinic, other than psychiatric department?	Number	139	(9.4)	64	(7.7)
DIABETES_impu_new[3]	Do you have, or have you had diabetes?	0 : No 1 : Yes, now 2 : Yes, previously	98	(6.6)	52	(6.3)

[1]Only used for analysis of blood pressure
[2]Only used for analysis of cholesterol
[3]Combination of several variables from Tromsø 7

Supplementary table 4: Achievement of treatment goal for HbA1c for participants with diabetes in the different CHD disease groups

	Diabetic population, n	Achieved treatment goal for HbA1c, n (%)
Coronary heart disease	214	91 (42.5)
Myocardial infarction	123	50 (40.7)
Percutaneous coronary intervention/ Coronary artery bypass surgery	80	34 (42.5)
Angina pectoris	11	7 (63.6)

Supplementary table 5: Results from propensity score matching of the ten imputed datasets for the logistic regression analysis of the association between use of lipid-lowering drugs and achieving the treatment goal for LDL-cholesterol

Dataset 1						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		252	1126	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.89 (13.15)	69.40 (9.72)	0.130
SEX_T7, n (%)			0.390			0.209
1	193 (55.9)	836 (74.2)		163 (64.7)	836 (74.2)	
BMI, mean (SD)	28.26 (4.92)	28.41 (4.35)	0.033	28.36 (4.50)	28.41 (4.35)	0.011
HEART_FAILURE_T7, n (%)			0.197			0.145
0	283 (82.0)	841 (74.6)		202 (80.2)	840 (74.6)	
1	30 (8.7)	114 (10.1)		23 (9.1)	114 (10.1)	
2	32 (9.3)	172 (15.3)		27 (10.7)	172 (15.3)	
ATRIAL_FIBRILLATION_T7, n (%)			0.142			0.067
0	236 (68.4)	842 (74.7)		181 (71.8)	842 (74.8)	
1	65 (18.8)	164 (14.6)		41 (16.3)	163 (14.5)	
2	44 (12.8)	121 (10.7)		30 (11.9)	121 (10.7)	
STROKE_T7, n (%)			0.074			0.038
2	41 (11.9)	162 (14.4)		33 (13.1)	162 (14.4)	
KIDNEY_DISEASE_T7, n (%)			0.137			0.128
0	282 (81.7)	977 (86.7)		207 (82.1)	977 (86.8)"	
1	35 (10.1)	87 (7.7)		26 (10.3)	86 (7.6)	
2	28 (8.1)	63 (5.6)		19 (7.5)	63 (5.6)	
CANCER_T7, n (%)			0.022			0.050
0	279 (80.9)	920 (81.6)		201 (79.8)	919 (81.6)	
1	24 (7.0)	73 (6.5)		17 (6.7)	73 (6.5)	
2	42 (12.2)	134 (11.9)		34 (13.5)	134 (11.9)	
DIABETES_impu_new, n (%)			0.096			0.064
0	274 (79.4)	889 (78.9)		200 (79.4)	888 (78.9)	
1	51 (14.8)	192 (17.0)		39 (15.5)	192 (17.1)	
2	20 (5.8)	46 (4.1)		13 (5.2)	46 (4.1)	
Cons_GP_Times_impu, mean (SD)	4.44 (6.03)	4.25 (5.31)	0.035	4.33 (5.90)	4.19 (5.01)	0.025
Cons_Emergency_Times_impu, mean (SD)	0.44 (0.88)	0.31 (0.74)	0.165	0.37 (0.76)	0.31 (0.74)	0.083
Cons_Hospital_Times_impu, mean (SD)	0.43 (1.26)	0.43 (0.90)	0.009	0.43 (1.35)	0.42 (0.90)	0.005
Cons_Specialist_Times_impu, mean (SD)	0.63 (1.85)	0.47 (2.49)	0.073	0.53 (1.67)	0.47 (2.49)	0.026
Cons_Clinic_Times_impu, mean (SD)	1.74 (7.48)	1.14 (4.74)	0.095	1.60 (7.14)	1.14 (4.75)	0.075
Alcohol_frequency_impu, n (%)			0.150			0.142
1	34 (9.9)	121 (10.7)		23 (9.1)	121 (10.7)	

2	85 (24.6)	209 (18.5)		60 (23.8)	208 (18.5)	
3	129 (37.4)	462 (41.0)		94 (37.3)	462 (41.0)	
4	69 (20.0)	243 (21.6)		53 (21.0)	243 (21.6)	
5	28 (8.1)	92 (8.2)		22 (8.7)	92 (8.2)	
Alcohol_units_impu, n (%)			0.069			0.071
0	36 (10.4)	119 (10.6)		23 (9.1)	119 (10.6)	
1	174 (50.4)	542 (48.1)		126 (50.0)	541 (48.0)	
2	102 (29.6)	367 (32.6)		78 (31.0)	367 (32.6)	
3	33 (9.6)	99 (8.8)		25 (9.9)	99 (8.8)	
Alcohol_units_6_impu, n (%)			0.117			0.146
1	188 (54.5)	662 (58.7)		133 (52.8)	662 (58.8)	
2	116 (33.6)	364 (32.3)		89 (35.3)	363 (32.2)	
3	32 (9.3)	77 (6.8)		23 (9.1)	77 (6.8)	
4	7 (2.0)	21 (1.9)		5 (2.0)	21 (1.9)	
5	2 (0.6)	3 (0.3)		2 (0.8)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.245
1	57 (16.5)	139 (12.3)		43 (17.1)	139 (12.3)	
2	12 (3.5)	19 (1.7)		7 (2.8)	19 (1.7)	
3	167 (48.4)	711 (63.1)		129 (51.2)	710 (63.1)	
4	109 (31.6)	258 (22.9)		73 (29.0)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.037			0.053
1	22 (6.4)	67 (5.9)		17 (6.7)	67 (6.0)	
2	1 (0.3)	2 (0.2)		1 (0.4)	2 (0.2)	
3	19 (5.5)	57 (5.1)		13 (5.2)	57 (5.1)	
4	303 (87.8)	1001 (88.8)		221 (87.7)	1000 (88.8)	
Cod_liver_oil_omega3_impu, n (%)			0.100			0.089
0	261 (75.7)	824 (73.1)		189 (75.0)	823 (73.1)	
1	44 (12.8)	144 (12.8)		34 (13.5)	144 (12.8)	
2	15 (4.3)	46 (4.1)		10 (4.0)	46 (4.1)	
3	25 (7.2)	113 (10.0)		19 (7.5)	113 (10.0)	
FRUIT_UNITS_T7, mean (SD)	1.72 (1.35)	1.96 (1.71)	0.157	1.73 (1.39)	1.92 (1.28)	0.143
RED_MEAT_T7, n (%)			0.066			0.095
1	24 (7.0)	74 (6.6)		14 (5.6)	74 (6.6)	
2	76 (22.0)	250 (22.2)		54 (21.4)	250 (22.2)	
3	216 (62.6)	723 (64.2)		167 (66.3)	722 (64.1)	
4	26 (7.5)	68 (6.0)		16 (6.3)	68 (6.0)	
5	3 (0.9)	12 (1.1)		1 (0.4)	12 (1.1)	
FRUITS_VEG_BERRY_T7, n (%)			0.095			0.110
1	4 (1.2)	12 (1.1)		1 (0.4)	12 (1.1)	
2	15 (4.3)	45 (4.0)		10 (4.0)	45 (4.0)	
3	66 (19.1)	259 (23.0)		54 (21.4)	259 (23.0)	
4	101 (29.3)	313 (27.8)		79 (31.3)	312 (27.7)	
5	159 (46.1)	498 (44.2)"		108 (42.9)	498 (44.2)	

LEAN_FISH_T7, n (%)			0.231			0.102
1	24 (7.0)	28 (2.5)		10 (4.0)	28 (2.5)	
2	50 (14.5)	153 (13.6)		38 (15.1)	153 (13.6)	
3	224 (64.9)	801 (71.1)		175 (69.4)	800 (71.0)	
4	41 (11.9)	134 (11.9)		27 (10.7)	134 (11.9)	
5	6 (1.7)	11 (1.0)		2 (0.8)	11 (1.0)	
FAT_FISH_T7, n (%)			0.151			0.098
1	49 (14.2)	113 (10.0)		31 (12.3)	112 (9.9)	
2	116 (33.6)	392 (34.8)		81 (32.1)	392 (34.8)	
3	153 (44.3)	550 (48.8)		125 (49.6)	550 (48.8)	
4	19 (5.5)	54 (4.8)		10 (4.0)	54 (4.8)	
5	8 (2.3)	18 (1.6)		5 (2.0)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_ T7, n (%)			0.108			0.048
1	86 (24.9)	232 (20.6)		55 (21.8)	231 (20.5)	
2	179 (51.9)	625 (55.5)		140 (55.6)	625 (55.5)	
3	72 (20.9)	247 (21.9)		53 (21.0)	247 (21.9)	
4	8 (2.3)	23 (2.0)		4 (1.6)	23 (2.0)	
EXERCISE_T7, n (%)			0.175			0.144
1	45 (13.0)	107 (9.5)		29 (11.5)	107 (9.5)	
2	54 (15.7)	142 (12.6)		39 (15.5)	142 (12.6)	
3	51 (14.8)	155 (13.8)		38 (15.1)	155 (13.8)	
4	111 (32.2)	434 (38.5)		82 (32.5)	433 (38.5)	
5	84 (24.3)	289 (25.6)		64 (25.4)	289 (25.7)	
Dataset 2						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		261	1124	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.75 (12.84)	69.38 (9.72)	0.143
SEX_T7, n (%)			0.390			0.247
1	193 (55.9)	836 (74.2)		164 (62.8)	834 (74.2)	
BMI, mean (SD)	28.27 (4.92)	28.43 (4.41)	0.036	28.52 (4.91)	28.42 (4.40)	0.021
HEART_FAILURE_T7, n (%)			0.182			0.147
0	282 (81.7)	838 (74.4)		210 (80.5)	837 (74.5)	
1	25 (7.2)	104 (9.2)		20 (7.7)	103 (9.2)	
2	38 (11.0)	185 (16.4)		31 (11.9)	184 (16.4)	
ATRIAL_FIBRILLATION_T7, n (%)			0.140			0.081
0	236 (68.4)	840 (74.5)		187 (71.6)	839 (74.6)	
1	65 (18.8)	162 (14.4)		45 (17.2)	161 (14.3)	
2	44 (12.8)	125 (11.1)		29 (11.1)	124 (11.0)"	
STROKE_T7, n (%)			0.069			0.062
2	43 (12.5)	167 (14.8)		33 (12.6)	166 (14.8)	
KIDNEY_DISEASE_T7, n (%)			0.173			0.155

0	278 (80.6)	977 (86.7)		213 (81.6)	976 (86.8)	
1	40 (11.6)	99 (8.8)		28 (10.7)	97 (8.6)	
2	27 (7.8)	51 (4.5)		20 (7.7)	51 (4.5)	
CANCER_T7, n (%)			0.039			0.083
0	277 (80.3)	922 (81.8)		206 (78.9)	919 (81.8)	
1	28 (8.1)	84 (7.5)		20 (7.7)	84 (7.5)	
2	40 (11.6)	121 (10.7)		35 (13.4)	121 (10.8)	
DIABETES_impu_new, n (%)			0.065			0.087
0	273 (79.1)	887 (78.7)		209 (80.1)	886 (78.8)	
1	54 (15.7)	194 (17.2)		38 (14.6)	192 (17.1)	
2	18 (5.2)	46 (4.1)		14 (5.4)	46 (4.1)	
Cons_GP_Times_impu, mean (SD)	3.99 (4.80)	4.15 (5.05)	0.034	3.98 (4.32)	4.09 (4.73)	0.026
Cons_Emergency_Times_impu, mean (SD)	0.41 (0.89)	0.29 (0.71)	0.149	0.37 (0.79)	0.29 (0.71)	0.105
Cons_Hospital_Times_impu, mean (SD)	0.42 (1.24)	0.43 (0.90)	0.010	0.41 (1.33)	0.43 (0.90)	0.012
Cons_Specialist_Times_impu, mean (SD)	0.49 (1.39)	0.46 (2.52)	0.016	0.44 (1.18)	0.46 (2.52)	0.010
Cons_Clinic_Times_impu, mean (SD)	1.45 (4.89)	1.22 (4.78)	0.048	1.32 (2.84)	1.22 (4.78)	0.025
Alcohol_frequency_impu, n (%)			0.152			0.151
1	34 (9.9)	121 (10.7)		28 (10.7)	121 (10.8)	
2	85 (24.6)	209 (18.5)		60 (23.0)	208 (18.5)	
3	128 (37.1)	462 (41.0)		96 (36.8)	461 (41.0)	
4	69 (20.0)	243 (21.6)		50 (19.2)	243 (21.6)	
5	29 (8.4)	92 (8.2)		27 (10.3)	91 (8.1)	
Alcohol_units_impu, n (%)			0.074			0.078
0	36 (10.4)	119 (10.6)		30 (11.5)	119 (10.6)	
1	176 (51.0)	542 (48.1)		130 (49.8)	539 (48.0)	
2	101 (29.3)	367 (32.6)		76 (29.1)	367 (32.7)	
3	32 (9.3)	99 (8.8)		25 (9.6)	99 (8.8)	
Alcohol_units_6_impu, n (%)			0.107			0.095
1	188 (54.5)	662 (58.7)		147 (56.3)	661 (58.8)	
2	120 (34.8)	362 (32.1)		86 (33.0)	360 (32.0)	
3	28 (8.1)	75 (6.7)		20 (7.7)	75 (6.7)	
4	6 (1.7)	23 (2.0)		5 (1.9)	23 (2.0)	
5	3 (0.9)	5 (0.4)		3 (1.1)	5 (0.4)	
Smoke_impu, n (%)			0.305			0.243
1	57 (16.5)	139 (12.3)		45 (17.2)	139 (12.4)	
2	12 (3.5)	19 (1.7)		7 (2.7)	19 (1.7)	
3	167 (48.4)	711 (63.1)		134 (51.3)	709 (63.1)	
4	109 (31.6)	258 (22.9		75 (28.7)	257 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.053			0.062
1	22 (6.4)	67 (5.9)		16 (6.1)	67 (6.0)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	58 (5.1)		14 (5.4)	58 (5.2)	

4	303 (87.8)	1001 (88.8)		230 (88.1)	998 (88.8)	
Cod_liver_oil_omega3_impu, n (%)			0.099			0.045
0	261 (75.7)	825 (73.2)		195 (74.7)	823 (73.2)	
1	44 (12.8)	142 (12.6)		33 (12.6)	142 (12.6)	
2	15 (4.3)	47 (4.2)		10 (3.8)	47 (4.2)	
3	25 (7.2)	113 (10.0)		23 (8.8)	112 (10.0)	
FRUIT_UNITS_T7, mean (SD)	1.80 (1.49)	1.98 (1.72)	0.112	1.82 (1.54)	1.94 (1.26)	0.085
RED_MEAT_T7, n (%)			0.088			0.122
1	24 (7.0)	72 (6.4)		18 (6.9)	72 (6.4)	
2	73 (21.2)	253 (22.4)		53 (20.3)	253 (22.5)	
3	218 (63.2)	721 (64.0)		169 (64.8)	719 (64.0)	
4	27 (7.8)	67 (5.9)		20 (7.7)	67 (6.0)	
5	3 (0.9)	14 (1.2)		1 (0.4)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.097			0.080
1	3 (0.9)	12 (1.1)		2 (0.8)	12 (1.1)	
2	14 (4.1)	49 (4.3)		9 (3.4)	49 (4.4)	
3	65 (18.8)	253 (22.4)		54 (20.7)	253 (22.5)	
4	103 (29.9)	313 (27.8)		73 (28.0)	312 (27.8)	
5	160 (46.4)	500 (44.4)		123 (47.1)	498 (44.3)	
LEAN_FISH_T7, n (%)			0.223			0.124
1	23 (6.7)	28 (2.5)		12 (4.6)	28 (2.5)	
2	50 (14.5)	151 (13.4)		37 (14.2)	151 (13.4)	
3	229 (66.4)	802 (71.2)		180 (69.0)	800 (71.2)	
4	36 (10.4)	133 (11.8)		30 (11.5)	132 (11.7)	
5	7 (2.0)	13 (1.2)		2 (0.8)	13 (1.2)	
FAT_FISH_T7, n (%)			0.156			0.065
1	51 (14.8)	113 (10.0)		29 (11.1)	112 (10.0)	
2	116 (33.6)	393 (34.9)		88 (33.7)	393 (35.0)	
3	156 (45.2)	551 (48.9)		130 (49.8)	549 (48.8)	
4	15 (4.3)	54 (4.8)		10 (3.8)	54 (4.8)	
5	7 (2.0)	16 (1.4)		4 (1.5)	16 (1.4)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.069			0.050
1	79 (22.9)	241 (21.4)		57 (21.8)	238 (21.2)	
2	182 (52.8)	623 (55.3)		139 (53.3)	623 (55.4)	
3	75 (21.7)	242 (21.5)		59 (22.6)	242 (21.5)	
4	9 (2.6)	21 (1.9)		6 (2.3)	21 (1.9)	
EXERCISE_T7, n (%)			0.176			0.127
1	43 (12.5)	102 (9.1)		26 (10.0)	102 (9.1)	
2	54 (15.7)	143 (12.7)		41 (15.7)	142 (12.6)	
3	51 (14.8)	153 (13.6)		36 (13.8)	153 (13.6)	
4	111 (32.2)	437 (38.8)		87 (33.3)	435 (38.7)	
5	86 (24.9)	292 (25.9)		71 (27.2)	292 (26.0)	
Dataset 3						

	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		259	1127	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	68.00 (12.72)	69.41 (9.72	0.124
SEX_T7, n (%)			0.390			0.212
1	193 (55.9)	836 (74.2)		167 (64.5)	836 (74.2)	
BMI, mean (SD)	28.26 (4.94)	28.41 (4.35)	0.031	28.49 (4.70)	28.41 (4.35)	0.018
HEART_FAILURE_T7, n (%)			0.191			0.190
0	279 (80.9)	844 (74.9)		213 (82.2)	844 (74.9)	
1	33 (9.6)	104 (9.2)		20 (7.7)	104 (9.2)	
2	33 (9.6)	179 (15.9)		26 (10.0)	179 (15.9)	
ATRIAL_FIBRILLATION_T7, n (%)			0.153			0.093
0	238 (69.0)	844 (74.9)		187 (72.2)	844 (74.9)	
1	69 (20.0)	162 (14.4)		46 (17.8)	162 (14.4)	
2	38 (11.0)	121 (10.7)		26 (10.0)	121 (10.7)	
STROKE_T7, n (%)			0.065			0.048
2	42 (12.2)	162 (14.4)		33 (12.7)	162 (14.4)	
KIDNEY_DISEASE_T7, n (%)			0.143			0.090
0	282 (81.7)	976 (86.6)		216 (83.4)	976 (86.6)	
1	36 (10.4)	96 (8.5)		27 (10.4)	96 (8.5)	
2	27 (7.8)	55 (4.9)		16 (6.2)	55 (4.9)	
CANCER_T7, n (%)			0.028			0.053
0	280 (81.2)	919 (81.5)		206 (79.5)	919 (81.5)	
1	24 (7.0)	83 (7.4)		22 (8.5)	83 (7.4)	
2	41 (11.9)	125 (11.1)		31 (12.0)	125 (11.1)	
DIABETES_impu_new, n (%)			0.114			0.106
0	274 (79.4)	887 (78.7)		208 (80.3)	887 (78.7)	
1	52 (15.1)	200 (17.7)		38 (14.7)	200 (17.7)	
2	19 (5.5)	40 (3.5)		13 (5.0)	40 (3.5)	
Cons_GP_Times_impu, mean (SD)	4.33 (6.06)	4.14 (4.77)	0.036	3.99 (5.30)	4.14 (4.77)	0.028
Cons_Emergency_Times_impu, mean (SD)	0.39 (0.81)	0.30 (0.73)	0.116	0.31 (0.72)	0.30 (0.73)	0.008
Cons_Hospital_Times_impu, mean (SD)	0.48 (1.43)	0.43 (0.91)	0.040	0.42 (1.26)	0.43 (0.91)	0.012
Cons_Specialist_Times_impu, mean (SD)	0.61 (1.78)	0.48 (2.56)	0.059	0.62 (1.74)	0.48 (2.56)	0.061
Cons_Clinic_Times_impu, mean (SD)	1.12 (2.48)	1.07 (4.17)	0.012	1.18 (2.61)	1.07 (4.17)	0.030
Alcohol_frequency_impu, n (%)			0.152			0.146
1	34 (9.9)	121 (10.7)		23 (8.9)	121 (10.7)	
2	85 (24.6)	209 (18.5)		62 (23.9)	209 (18.5)	
3	128 (37.1)	462 (41.0)		101 (39.0)	462 (41.0)	

4	69 (20.0)	243 (21.6)		50 (19.3)	243 (21.6)	
5	29 (8.4)	92 (8.2)		23 (8.9)	92 (8.2)	
Alcohol_units_impu, n (%)			0.074			0.078
0	36 (10.4)	119 (10.6)		24 (9.3)	119 (10.6)	
1	175 (50.7)	541 (48.0)		132 (51.0)	541 (48.0)	
2	101 (29.3)	367 (32.6)		78 (30.1)	367 (32.6)	
3	33 (9.6)	100 (8.9)		25 (9.7)	100 (8.9)	
Alcohol_units_6_impu, n (%)			0.129			0.126
1	187 (54.2)	664 (58.9)		139 (53.7)	664 (58.9)	
2	121 (35.1)	363 (32.2)		93 (35.9)	363 (32.2)	
3	28 (8.1)	74 (6.6)		20 (7.7)	74 (6.6)	
4	6 (1.7)	23 (2.0)		5 (1.9)	23 (2.0)	
5	3 (0.9)	3 (0.3)		2 (0.8)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.195
1	57 (16.5)	139 (12.3)		37 (14.3)	139 (12.3)	
2	12 (3.5)	19 (1.7)		8 (3.1)	19 (1.7)	
3	167 (48.4)	711 (63.1)		140 (54.1)	711 (63.1)	
4	109 (31.6)	258 (22.9)		74 (28.6)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.054			0.072
1	22 (6.4)	67 (5.9)		16 (6.2)	67 (5.9)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	57 (5.1)		11 (4.2)	57 (5.1)	
4	303 (87.8)	1002 (88.9)		231 (89.2)	1002 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.109			0.106
0	259 (75.1)	821 (72.8)		196 (75.7)	821 (72.8)	
1	46 (13.3)	142 (12.6)		34 (13.1)	142 (12.6)	
2	14 (4.1)	44 (3.9)		9 (3.5)	44 (3.9)	
3	26 (7.5)	120 (10.6)		20 (7.7)	120 (10.6)	
FRUIT_UNITS_T7, mean (SD)	1.72 (1.33)	1.97 (1.71)	0.164	1.76 (1.42)	1.97 (1.71)	0.131
RED_MEAT_T7, n (%)			0.079			0.075
1	24 (7.0)	75 (6.7)		19 (7.3)	75 (6.7)	
2	79 (22.9)	256 (22.7)		65 (25.1)	256 (22.7)	
3	213 (61.7)	718 (63.7)		159 (61.4)	718 (63.7)	
4	26 (7.5)	65 (5.8)		14 (5.4)	65 (5.8)	
5	3 (0.9)	13 (1.2)		2 (0.8)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.105			0.062
1	3 (0.9)	12 (1.1)		2 (0.8)	12 (1.1)	
2	13 (3.8)	45 (4.0)		9 (3.5)	45 (4.0)	
3	65 (18.8)	258 (22.9)		56 (21.6)	258 (22.9)	
4	101 (29.3)	312 (27.7)		77 (29.7)	312 (27.7)	
5	163 (47.2)	500 (44.4)		115 (44.4)	500 (44.4)	
LEAN_FISH_T7, n (%)			0.218			0.095
1	23 (6.7)	28 (2.5)		9 (3.5)	28 (2.5)	

2	55 (15.9)	155 (13.8)		42 (16.2)	155 (13.8)	
3	227 (65.8)	799 (70.9)		176 (68.0)	799 (70.9)	
4	36 (10.4)	133 (11.8)		29 (11.2)	133 (11.8)	
5	4 (1.2)	12 (1.1)		3 (1.2)	12 (1.1)	
FAT_FISH_T7, n (%)			0.145			0.135
1	52 (15.1)	117 (10.4)		38 (14.7)	117 (10.4)	
2	116 (33.6)	390 (34.6)		86 (33.2)	390 (34.6)	
3	157 (45.5)	548 (48.6)		121 (46.7)	548 (48.6)	
4	14 (4.1)	54 (4.8)		10 (3.9)	54 (4.8)	
5	6 (1.7)	18 (1.6)		4 (1.5)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_ T7, n (%)			0.078			0.081
1	83 (24.1)	236 (20.9)		63 (24.3)	236 (20.9)	
2	180 (52.2)	622 (55.2)		136 (52.5)	622 (55.2)	
3	75 (21.7)	246 (21.8)		55 (21.2)	246 (21.8)	
4	7 (2.0)	23 (2.0)		5 (1.9)	23 (2.0)	
EXERCISE_T7, n (%)			0.179			0.177
1	45 (13.0)	107 (9.5)		31 (12.0)	107 (9.5)	
2	53 (15.4)	141 (12.5)		40 (15.4)	141 (12.5)	
3	52 (15.1)	154 (13.7)		39 (15.1)	154 (13.7)	
4	110 (31.9)	436 (38.7)		80 (30.9)	436 (38.7)	
5	85 (24.6)	289 (25.6)		69 (26.6)	289 (25.6)	
Dataset 4						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		244	1126	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	68.00 (12.67)	69.40 (9.72)	0.124
SEX_T7, n (%)			0.390			0.285
1	193 (55.9)	836 (74.2)		149 (61.1)	836 (74.2)	
BMI, mean (SD)	28.26 (4.94)	28.43 (4.39)	0.035	28.61 (4.82)	28.42 (4.39)	0.041
HEART_FAILURE_T7, n (%)			0.212			0.150
0	280 (81.2)	840 (74.5)		197 (80.7)	839 (74.5)	
1	32 (9.3)	99 (8.8)		16 (6.6)	99 (8.8)	
2	33 (9.6)	188 (16.7)		31 (12.7)	188 (16.7)	
ATRIAL_FIBRILLATION_T7, n (%)			0.151			0.137
0	236 (68.4)	843 (74.8)		173 (70.9)	843 (74.9)	
1	67 (19.4)	161 (14.3)		47 (19.3)	160 (14.2)	
2	42 (12.2)	123 (10.9)		24 (9.8)	123 (10.9)	
STROKE_T7, n (%)			0.072			0.082
2	42 (12.2)	165 (14.6)		29 (11.9)	165 (14.7)	
KIDNEY_DISEASE_T7, n (%)			0.124			0.035
0	284 (82.3)	978 (86.8)		209 (85.7)	978 (86.9)	
1	37 (10.7)	90 (8.0)		21 (8.6)	89 (7.9)	

2	24 (7.0)	59 (5.2)		14 (5.7)	59 (5.2)	
CANCER_T7, n (%)			0.035			0.049
0	279 (80.9)	919 (81.5)		196 (80.3)	918 (81.5)	
1	27 (7.8)	78 (6.9)		16 (6.6)	78 (6.9)	
2	39 (11.3)	130 (11.5)		32 (13.1)	130 (11.5)	
DIABETES_impu_new, n (%)			0.064			0.056
0	276 (80.0)	889 (78.9)		195 (79.9)	888 (78.9)	
1	53 (15.4)	195 (17.3)		38 (15.6)	195 (17.3)	
2	16 (4.6)	43 (3.8)		11 (4.5)	43 (3.8)	
Cons_GP_Times_impu, mean (SD)	4.59 (6.65)	4.18 (5.04)	0.070	4.31 (6.35)	4.17 (5.03)	0.024
Cons_Emergency_Times_impu, mean (SD)	0.39 (0.96)	0.30 (0.73)	0.104	0.31 (0.89)	0.30 (0.73)	0.011
Cons_Hospital_Times_impu, mean (SD)	0.44 (1.25)	0.43 (0.90)	0.004	0.39 (1.33)	0.43 (0.90)	0.033
Cons_Specialist_Times_impu, mean (SD)	0.54 (1.62)	0.44 (2.44)	0.051	0.48 (1.39)	0.44 (2.44)	0.018
Cons_Clinic_Times_impu, mean (SD)	1.04 (2.38)	1.09 (4.16)	0.014	1.02 (2.49)	1.09 (4.16)	0.021
Alcohol_frequency_impu, n (%)			0.150			0.133
1	34 (9.9)	121 (10.7)		25 (10.2)	121 (10.7)	
2	85 (24.6)	209 (18.5)		58 (23.8)	208 (18.5)	
3	129 (37.4)	462 (41.0)		94 (38.5)	462 (41.0)	
4	69 (20.0)	243 (21.6)		47 (19.3)	243 (21.6)	
5	28 (8.1)	92 (8.2)		20 (8.2)	92 (8.2)	
Alcohol_units_impu, n (%)			0.076			0.061
0	36 (10.4)	121 (10.7)		26 (10.7)	121 (10.7)	
1	176 (51.0)	540 (47.9)		123 (50.4)	539 (47.9)	
2	101 (29.3)	367 (32.6)		73 (29.9)	367 (32.6)	
3	32 (9.3)	99 (8.8)		22 (9.0)	99 (8.8)	
Alcohol_units_6_impu, n (%)			0.103			0.065
1	187 (54.2)	662 (58.7)		137 (56.1)	662 (58.8)	
2	122 (35.4)	366 (32.5)		84 (34.4)	365 (32.4)	
3	27 (7.8)	74 (6.6)		16 (6.6)	74 (6.6)	
4	7 (2.0)	22 (2.0)		6 (2.5)	22 (2.0)	
5	2 (0.6)	3 (0.3)		1 (0.4)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.271
1	57 (16.5)	139 (12.3)		39 (16.0)	139 (12.3)	
2	12 (3.5)	19 (1.7)		4 (1.6)	19 (1.7)	
3	167 (48.4)	711 (63.1)		122 (50.0)	710 (63.1)	
4	109 (31.6)	258 (22.9)		79 (32.4)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.034			0.096
1	22 (6.4)	67 (5.9)		12 (4.9)	67 (6.0)	
2	1 (0.3)	2 (0.2)		1 (0.4)	2 (0.2)	
3	19 (5.5)	58 (5.1)		9 (3.7)	58 (5.2)	
4	303 (87.8)	1000 (88.7)		222 (91.0)	999 (88.7)	

Cod_liver_oil_omega3_impu, n (%)			0.091			0.081
0	260 (75.4)	825 (73.2)		181 (74.2)	824 (73.2)	
1	45 (13.0)	145 (12.9)		35 (14.3)	145 (12.9)	
2	14 (4.1)	43 (3.8)		8 (3.3)	43 (3.8)	
3	26 (7.5)	114 (10.1)		20 (8.2)	114 (10.1)	
FRUIT_UNITS_T7, mean (SD)	1.74 (1.35)	1.95 (1.71)	0.142	1.76 (1.28)	1.92 (1.28)	0.127
RED_MEAT_T7, n (%)			0.068			0.090
1	24 (7.0)	70 (6.2)		14 (5.7)	70 (6.2)	
2	78 (22.6)	251 (22.3)		57 (23.4)	251 (22.3)	
3	214 (62.0)	722 (64.1)		156 (63.9)	721 (64.0)	
4	26 (7.5)	71 (6.3)		16 (6.6)	71 (6.3)	
5	3 (0.9)	13 (1.2)		1 (0.4)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.124			0.091
1	5 (1.4)	13 (1.2)		4 (1.6)	13 (1.2)	
2	14 (4.1)	44 (3.9)		11 (4.5)	44 (3.9)	
3	62 (18.0)	258 (22.9)		48 (19.7)	258 (22.9)	
4	101 (29.3)	313 (27.8)		71 (29.1)	312 (27.7)	
5	163 (47.2)	499 (44.3)		110 (45.1)	499 (44.3)	
LEAN_FISH_T7, n (%)			0.217			0.101
1	23 (6.7)	28 (2.5)		9 (3.7)	28 (2.5)	
2	53 (15.4)	150 (13.3)		37 (15.2)	150 (13.3)	
3	224 (64.9)	800 (71.0)		166 (68.0)	799 (71.0)	
4	41 (11.9)	135 (12.0)		30 (12.3)	135 (12.0)	
5	4 (1.2)	14 (1.2)		2 (0.8)	14 (1.2)	
FAT_FISH_T7, n (%)			0.156			0.124
1	50 (14.5)	114 (10.1)		28 (11.5)	113 (10.0)	
2	114 (33.0)	389 (34.5)		74 (30.3)	389 (34.5)	
3	158 (45.8)	553 (49.1)		124 (50.8)	553 (49.1)	
4	14 (4.1)	53 (4.7)		11 (4.5)	53 (4.7)	
5	9 (2.6)	18 (1.6)		7 (2.9)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.073			0.024
1	82 (23.8)	234 (20.8)		52 (21.3)	233 (20.7)	
2	180 (52.2)	615 (54.6)		134 (54.9)	615 (54.6)	
3	76 (22.0)	253 (22.4)		53 (21.7)	253 (22.5)	
4	7 (2.0)	25 (2.2)		5 (2.0)	25 (2.2)	
EXERCISE_T7, n (%)			0.166			0.126
1	43 (12.5)	104 (9.2)		27 (11.1)	104 (9.2)	
2	53 (15.4)	143 (12.7)		33 (13.5)	143 (12.7)	
3	52 (15.1)	156 (13.8)		40 (16.4)	156 (13.9)	
4	111 (32.2)	434 (38.5)		81 (33.2)	433 (38.5)	
5	86 (24.9)	290 (25.7)		63 (25.8)	290 (25.8)	
Dataset 5						
	Before matching			**After matching**		

	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		249	1126	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.91 (12.69)	69.40 (9.72)	0.132
SEX_T7, n (%)			0.390			0.243
1	193 (55.9)	836 (74.2)		157 (63.1)	836 (74.2)	
BMI, mean (SD)	28.23 (4.94)	28.42 (4.37)	0.042	28.31 (4.83)	28.42 (4.37)	0.024
HEART_FAILURE_T7, n (%)			0.190			0.133
0	282 (81.7)	838 (74.4)		199 (79.9)	837 (74.3)	
1	27 (7.8)	104 (9.2)		18 (7.2)	104 (9.2)	
2	36 (10.4)	185 (16.4)		32 (12.9)	185 (16.4)	
ATRIAL_FIBRILLATION_T7, n (%)			0.123			0.125
0	239 (69.3)	839 (74.4)		174 (69.9)	839 (74.5)	
1	64 (18.6)	162 (14.4)		47 (18.9)	161 (14.3)	
2	42 (12.2)	126 (11.2)		28 (11.2)	126 (11.2)	
STROKE_T7, n (%)			0.074			0.007
2	43 (12.5)	169 (15.0)		38 (15.3)	169 (15.0)	
KIDNEY_DISEASE_T7, n (%)			0.144			0.156
0	281 (81.4)	977 (86.7)		202 (81.1)	977 (86.8)	
1	39 (11.3)	91 (8.1)		27 (10.8)	90 (8.0)	
2	25 (7.2)	59 (5.2)		20 (8.0)	59 (5.2)	
CANCER_T7, n (%)			0.025			0.101
0	278 (80.6)	919 (81.5)		193 (77.5)	918 (81.5)	
1	26 (7.5)	81 (7.2)		21 (8.4)	81 (7.2)	
2	41 (11.9)	127 (11.3)		35 (14.1)	127 (11.3)	
DIABETES_impu_new, n (%)			0.043			0.084
0	275 (79.7)	891 (79.1)		195 (78.3)	890 (79.0)	
1	57 (16.5)	200 (17.7)		42 (16.9)	200 (17.8)	
2	13 (3.8)	36 (3.2)		12 (4.8)	36 (3.2)	
Cons_GP_Times_impu, mean (SD)	4.28 (5.56)	4.31 (5.47)	0.005	4.27 (5.41)	4.29 (5.43)	0.004
Cons_Emergency_Times_impu, mean (SD)	0.43 (0.87)	0.30 (0.73)	0.165	0.34 (0.74)	0.30 (0.73)	0.061
Cons_Hospital_Times_impu, mean (SD)	0.43 (1.27)	0.44 (0.92)	0.003	0.42 (1.14)	0.43 (0.91)	0.015
Cons_Specialist_Times_impu, mean (SD)	0.51 (1.43)	0.44 (2.45)	0.033	0.47 (1.34)	0.44 (2.45)	0.012
Cons_Clinic_Times_impu, mean (SD)	1.32 (4.93)	1.19 (4.81)	0.027	1.50 (5.66)	1.19 (4.82)	0.059
Alcohol_frequency_impu, n (%)			0.150			0.145
1	34 (9.9)	121 (10.7)		27 (10.8)	121 (10.7)	
2	85 (24.6)	209 (18.5)		58 (23.3)	208 (18.5)	
3	129 (37.4)	462 (41.0)		100 (40.2)	462 (41.0)	
4	69 (20.0)	243 (21.6)		43 (17.3)	243 (21.6)	

5	28 (8.1)	92 (8.2)		21 (8.4)	92 (8.2)	
Alcohol_units_impu, n (%)			0.075			0.112
0	36 (10.4)	119 (10.6)		27 (10.8)	119 (10.6)	
1	175 (50.7)	542 (48.1)		127 (51.0)	541 (48.0)	
2	101 (29.3)	367 (32.6)		69 (27.7)	367 (32.6)	
3	33 (9.6)	99 (8.8)		26 (10.4)	99 (8.8)	
Alcohol_units_6_impu, n (%)			0.091			0.115
1	189 (54.8)	664 (58.9)		140 (56.2)	664 (59.0)	
2	120 (34.8)	364 (32.3)		83 (33.3)	363 (32.2)	
3	27 (7.8)	74 (6.6)		20 (8.0)	74 (6.6)	
4	7 (2.0)	21 (1.9)		6 (2.4)	21 (1.9)	
5	2 (0.6)	4 (0.4)		0 (0.0)	4 (0.4)	
Smoke_impu, n (%)			0.305			0.197
1	57 (16.5)	139 (12.3)		39 (15.7)	139 (12.3)	
2	12 (3.5)	19 (1.7)		5 (2.0)	19 (1.7)	
3	167 (48.4)	711 (63.1)		133 (53.4)	710 (63.1)	
4	109 (31.6)	258 (22.9)		72 (28.9)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.053			0.080
1	22 (6.4)	68 (6.0)		15 (6.0)	68 (6.0)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	57 (5.1)		10 (4.0)	57 (5.1)	
4	303 (87.8)	1001 (88.8)		223 (89.6)	1000 (88.8)	
Cod_liver_oil_omega3_impu, n (%)			0.075			0.054
0	260 (75.4)	823 (73.0)		187 (75.1)	822 (73.0)	
1	43 (12.5)	145 (12.9)		31 (12.4)	145 (12.9)	
2	14 (4.1)	44 (3.9)		9 (3.6)	44 (3.9)	
3	28 (8.1)	115 (10.2)		22 (8.8)	115 (10.2)	
FRUIT_UNITS_T7, mean (SD)	1.74 (1.35)	1.98 (1.76	0.152	1.76 (1.41)	1.95 (1.35)	0.135
RED_MEAT_T7, n (%)			0.055			0.032
1	23 (6.7)	73 (6.5)		17 (6.8)	73 (6.5)	
2	80 (23.2)	255 (22.6)		55 (22.1)	255 (22.6)	
3	214 (62.0)	720 (63.9)		158 (63.5)	719 (63.9)	
4	24 (7.0)	65 (5.8)		16 (6.4)	65 (5.8)	
5	4 (1.2)	14 (1.2)		3 (1.2)	14 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.101			0.121
1	4 (1.2)	13 (1.2)		2 (0.8)	13 (1.2)	
2	15 (4.3)	47 (4.2)		13 (5.2)	47 (4.2)	
3	64 (18.6)	255 (22.6)		46 (18.5)	255 (22.6)	
4	101 (29.3)	313 (27.8)		69 (27.7)	312 (27.7)	
5	161 (46.7)	499 (44.3)		119 (47.8)	499 (44.3)	
LEAN_FISH_T7, n (%)			0.241			0.102
1	24 (7.0)	28 (2.5)		10 (4.0)	28 (2.5)	
2	53 (15.4)	153 (13.6)		35 (14.1)	153 (13.6)	

3	223 (64.6)	800 (71.0)		171 (68.7)	799 (71.0)	
4	38 (11.0)	134 (11.9)		29 (11.6)	134 (11.9)	
5	7 (2.0)	12 (1.1)		4 (1.6)	12 (1.1)	
FAT_FISH_T7, n (%)			0.138			0.110
1	50 (14.5)	115 (10.2)		27 (10.8)	114 (10.1)	
2	116 (33.6)	389 (34.5)		82 (32.9)	389 (34.5)	
3	157 (45.5)	550 (48.8)		126 (50.6)	550 (48.8)	
4	15 (4.3)	55 (4.9)		8 (3.2)	55 (4.9)	
5	7 (2.0)	18 (1.6)		6 (2.4)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.077			0.077
1	81 (23.5)	237 (21.0)		58 (23.3)	236 (21.0)	
2	176 (51.0)	615 (54.6)		127 (51.0)	615 (54.6)	
3	77 (22.3)	244 (21.7)		56 (22.5)	244 (21.7)	
4	11 (3.2)	31 (2.8)		8 (3.2)	31 (2.8)	
EXERCISE_T7, n (%)			0.169			0.180
1	42 (12.2)	103 (9.1)		33 (13.3)	103 (9.1)	
2	53 (15.4)	143 (12.7)		35 (14.1)	143 (12.7)	
3	54 (15.7)	153 (13.6)		35 (14.1)	153 (13.6)	
4	112 (32.5)	435 (38.6)		78 (31.3)	434 (38.5)	
5	84 (24.3)	293 (26.0)		68 (27.3)	293 (26.0)	
Dataset 6						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		248	1127	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.70 (12.36)	69.41 (9.72)	0.154
SEX_T7, n (%)			0.390			0.236
1	193 (55.9)	836 (74.2)		157 (63.3)	836 (74.2)	
BMI, mean (SD)	28.22 (4.91)	28.41 (4.36)	0.042	28.51 (4.93)	28.41 (4.36)	0.021
HEART_FAILURE_T7, n (%)			0.190			0.160
0	282 (81.7)	841 (74.6)		201 (81.0)	841 (74.6)	
1	31 (9.0)	116 (10.3)		21 (8.5)	116 (10.3)	
2	32 (9.3)	170 (15.1)		26 (10.5)	170 (15.1)	
ATRIAL_FIBRILLATION_T7, n (%)			0.133			0.073
0	240 (69.6)	840 (74.5)		177 (71.4)	840 (74.5)	
1	66 (19.1)	161 (14.3)		41 (16.5)	161 (14.3)	
2	39 (11.3)	126 (11.2)		30 (12.1)	126 (11.2)	
STROKE_T7, n (%)			0.052			0.036
2	44 (12.8)	164 (14.6)		33 (13.3)	164 (14.6)	
KIDNEY_DISEASE_T7, n (%)			0.145			0.086
0	283 (82.0)	978 (86.8)		208 (83.9)	978 (86.8)	
1	36 (10.4)	98 (8.7)		25 (10.1)	98 (8.7)	
2	26 (7.5)	51 (4.5)		15 (6.0)	51 (4.5)	

CANCER_T7, n (%)			0.019			0.076
0	280 (81.2)	922 (81.8)		198 (79.8)	922 (81.8)	
1	27 (7.8)	87 (7.7)		18 (7.3)	87 (7.7)	
2	38 (11.0)	118 (10.5)		32 (12.9)	118 (10.5)	
DIABETES_impu_new, n (%)			0.104			0.114
0	273 (79.1)	887 (78.7)		196 (79.0)	887 (78.7)	
1	52 (15.1)	196 (17.4)		37 (14.9)	196 (17.4)	
2	20 (5.8)	44 (3.9)		15 (6.0)	44 (3.9)	
Cons_GP_Times_impu, mean (SD)	4.19 (5.30)	4.14 (4.62)	0.009	4.28 (5.72)	4.14 (4.62)	0.027
Cons_Emergency_Times_impu, mean (SD)	0.39 (0.81)	0.30 (0.72)	0.129	0.34 (0.73)	0.30 (0.72)	0.066
Cons_Hospital_Times_impu, mean (SD)	0.43 (1.26)	0.43 (0.91)	0.002	0.47 (1.41)	0.43 (0.91)	0.033
Cons_Specialist_Times_impu, mean (SD)	0.60 (1.69)	0.52 (2.67)	0.033	0.55 (1.47)	0.52 (2.67)	0.013
Cons_Clinic_Times_impu, mean (SD)	1.29 (4.79)	1.28 (5.18)	0.001	1.25 (5.35)	1.28 (5.18)	0.006
Alcohol_frequency_impu, n (%)			0.150			0.159
1	34 (9.9)	121 (10.7)		25 (10.1)	121 (10.7)	
2	85 (24.6)	209 (18.5)		62 (25.0)	209 (18.5)	
3	129 (37.4)	462 (41.0)		92 (37.1)	462 (41.0)	
4	69 (20.0)	243 (21.6)		49 (19.8)	243 (21.6)	
5	28 (8.1)	92 (8.2)		20 (8.1)	92 (8.2)	
Alcohol_units_impu, n (%)			0.074			0.038
0	36 (10.4)	119 (10.6)		25 (10.1)	119 (10.6)	
1	175 (50.7)	541 (48.0)		121 (48.8)	541 (48.0)	
2	101 (29.3)	367 (32.6)		78 (31.5)	367 (32.6)	
3	33 (9.6)	100 (8.9)		24 (9.7)	100 (8.9)	
Alcohol_units_6_impu, n (%)			0.078			0.100
1	191 (55.4)	663 (58.8)		139 (56.0)	663 (58.8)	
2	118 (34.2)	363 (32.2)		82 (33.1)	363 (32.2)	
3	26 (7.5)	75 (6.7)		21 (8.5)	75 (6.7)	
4	8 (2.3)	22 (2.0)		4 (1.6)	22 (2.0)	
5	2 (0.6)	4 (0.4)		2 (0.8)	4 (0.4)	
Smoke_impu, n (%)			0.305			0.198
1	57 (16.5)	139 (12.3)		39 (15.7)	139 (12.3)	
2	12 (3.5)	19 (1.7)		7 (2.8)	19 (1.7)	
3	167 (48.4)	711 (63.1)		133 (53.6)	711 (63.1)	
4	109 (31.6)	258 (22.9)		69 (27.8)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.053			0.067
1	22 (6.4)	67 (5.9)		16 (6.5)	67 (5.9)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	58 (5.1)		13 (5.2)	58 (5.1)	
4	303 (87.8)	1001 (88.8)		218 (87.9)	1001 (88.8)	
Cod_liver_oil_omega3_impu, n (%)			0.085			0.118

0	261 (75.7)	820 (72.8)		188 (75.8)	820 (72.8)	
1	43 (12.5)	146 (13.0)		33 (13.3)	146 (13.0)	
2	14 (4.1)	47 (4.2)		10 (4.0)	47 (4.2)	
3	27 (7.8)	114 (10.1)		17 (6.9)	114 (10.1)	
FRUIT_UNITS_T7, mean (SD)	1.70 (1.34)	1.96 (1.71)	0.169	1.81 (1.44)	1.96 (1.71)	0.099
RED_MEAT_T7, n (%)			0.089			0.115
1	23 (6.7)	70 (6.2)		11 (4.4)	70 (6.2)	
2	76 (22.0)	255 (22.6)		57 (23.0)	255 (22.6)	
3	214 (62.0)	723 (64.2)		158 (63.7)	723 (64.2)	
4	28 (8.1)	67 (5.9)		20 (8.1)	67 (5.9)	
5	4 (1.2)	12 (1.1)		2 (0.8)	12 (1.1)	
FRUITS_VEG_BERRY_T7, n (%)			0.108			0.083
1	3 (0.9)	13 (1.2)		2 (0.8)	13 (1.2)	
2	17 (4.9)	46 (4.1)		10 (4.0)	46 (4.1)	
3	65 (18.8)	257 (22.8)		50 (20.2)	257 (22.8)	
4	99 (28.7)	312 (27.7)		75 (30.2)	312 (27.7)	
5	161 (46.7)	499 (44.3)		111 (44.8)	499 (44.3)	
LEAN_FISH_T7, n (%)			0.261			0.169
1	28 (8.1)	28 (2.5)		13 (5.2)	28 (2.5)	
2	51 (14.8)	152 (13.5)		36 (14.5)	152 (13.5)	
3	224 (64.9)	797 (70.7)		173 (69.8)	797 (70.7)	
4	37 (10.7)	134 (11.9)		24 (9.7)	134 (11.9)	
5	5 (1.4)	16 (1.4)		2 (0.8)	16 (1.4)	
FAT_FISH_T7, n (%)			0.180			0.122
1	55 (15.9)	114 (10.1)		34 (13.7)	114 (10.1)	
2	118 (34.2)	389 (34.5)		82 (33.1)	389 (34.5)	
3	152 (44.1)	549 (48.7)		118 (47.6)	549 (48.7)	
4	15 (4.3)	54 (4.8)		11 (4.4)	54 (4.8)	
5	5 (1.4)	21 (1.9)		3 (1.2)	21 (1.9)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.096			0.142
1	84 (24.3)	235 (20.9)		63 (25.4)	235 (20.9)	
2	176 (51.0)	621 (55.1)		122 (49.2)	621 (55.1)	
3	75 (21.7)	243 (21.6)		54 (21.8)	243 (21.6)	
4	10 (2.9)	28 (2.5)		9 (3.6)	28 (2.5)	
EXERCISE_T7, n (%)			0.186			0.194
1	46 (13.3)	105 (9.3)		32 (12.9)	105 (9.3)	
2	53 (15.4)	144 (12.8)		37 (14.9)	144 (12.8)	
3	51 (14.8)	154 (13.7)		36 (14.5)	154 (13.7)	
4	109 (31.6)	436 (38.7)		75 (30.2)	436 (38.7)	
5	86 (24.9)	288 (25.6)		68 (27.4)	288 (25.6)	
Dataset 7						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		250	1127	

AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.36 (13.22)	69.41 (9.72)	0.176
SEX_T7, n (%)						0.238
1	193 (55.9)	836 (74.2)	0.390	158 (63.2)	836 (74.2)	
BMI, mean (SD)	28.28 (4.95)	28.41 (4.35)	0.028	28.41 (4.65)	28.41 (4.35)	0.001
HEART_FAILURE_T7, n (%)			0.182			0.115
0	281 (81.4)	839 (74.4)		198 (79.2)	839 (74.4)	
1	29 (8.4)	110 (9.8)		21 (8.4)	110 (9.8)	
2	35 (10.1)	178 (15.8)		31 (12.4)	178 (15.8)	
ATRIAL_FIBRILLATION_T7, n (%)			0.138			0.128
0	238 (69.0)	844 (74.9)		173 (69.2)	844 (74.9)	
1	66 (19.1)	164 (14.6)		46 (18.4)	164 (14.6)	
2	41 (11.9)	119 (10.6)		31 (12.4)	119 (10.6)	
STROKE_T7, n (%)			0.060			0.041
2	42 (12.2)	160 (14.2)		32 (12.8)	160 (14.2)	
KIDNEY_DISEASE_T7, n (%)			0.144			0.151
0	281 (81.4)	977 (86.7)		203 (81.2)	977 (86.7)	
1	39 (11.3)	92 (8.2)		30 (12.0)	92 (8.2)	
2	25 (7.2)	58 (5.1)		17 (6.8)	58 (5.1)	
CANCER_T7, n (%)			0.046			0.092
0	278 (80.6)	921 (81.7)		200 (80.0)	921 (81.7)	
1	30 (8.7)	84 (7.5)		25 (10.0)	84 (7.5)	
2	37 (10.7)	122 (10.8)		25 (10.0)	122 (10.8)	
DIABETES_impu_new, n (%)			0.135			0.096
0	273 (79.1)	887 (78.7)		197 (78.8)	887 (78.7)	
1	53 (15.4)	205 (18.2)		41 (16.4)	205 (18.2)	
2	19 (5.5)	35 (3.1)		12 (4.8)	35 (3.1)	
Cons_GP_Times_impu, mean (SD)	4.48 (5.93)	4.11 (4.67)	0.069	4.22 (5.19)	4.11 (4.67)	0.024
Cons_Emergency_Times_impu, mean (SD)	0.39 (0.81)	0.31 (0.73)	0.107	0.34 (0.78)	0.31 (0.73)	0.047
Cons_Hospital_Times_impu, mean (SD)	0.44 (1.28)	0.43 (0.96)	0.012	0.36 (1.01)	0.43 (0.96)	0.076
Cons_Specialist_Times_impu, mean (SD)	0.66 (2.14)	0.52 (2.68)	0.055	0.66 (2.27)	0.52 (2.68)	0.057
Cons_Clinic_Times_impu, mean (SD)	1.26 (4.77)	1.17 (4.76)	0.019	1.32 (5.44)	1.17 (4.76)	0.029
Alcohol_frequency_impu, n (%)			0.157			0.150
1	34 (9.9)	121 (10.7)		23 (9.2)	121 (10.7)	
2	86 (24.9)	209 (18.5)		59 (23.6)	209 (18.5)	
3	128 (37.1)	462 (41.0)		91 (36.4)	462 (41.0)	
4	69 (20.0)	243 (21.6)		53 (21.2)	243 (21.6)	
5	28 (8.1)	92 (8.2)		24 (9.6)	92 (8.2)	
Alcohol_units_impu, n (%)			0.074			0.074
0	36 (10.4)	119 (10.6)		23 (9.2)	119 (10.6)	

1	175 (50.7)	541 (48.0)		127 (50.8)	541 (48.0)	
2	101 (29.3)	367 (32.6)		76 (30.4)	367 (32.6)	
3	33 (9.6)	100 (8.9)		24 (9.6)	100 (8.9)	
Alcohol_units_6_impu, n (%)			0.090			0.111
1	190 (55.1)	664 (58.9)		139 (55.6)	664 (58.9)	
2	119 (34.5)	362 (32.1)		83 (33.2)	362 (32.1)	
3	27 (7.8)	77 (6.8)		19 (7.6)	77 (6.8)	
4	7 (2.0)	21 (1.9)		7 (2.8)	21 (1.9)	
5	2 (0.6)	3 (0.3)		2 (0.8)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.197
1	57 (16.5)	139 (12.3)		37 (14.8)	139 (12.3)	
2	12 (3.5)	19 (1.7)		9 (3.6)	19 (1.7)	
3	167 (48.4)	711 (63.1)		136 (54.4)	711 (63.1)	
4	109 (31.6)	258 (22.9)		68 (27.2)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.054			0.086
1	22 (6.4)	67 (5.9)		18 (7.2)	67 (5.9)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	57 (5.1)		14 (5.6)	57 (5.1)	
4	303 (87.8)	1002 (88.9)		217 (86.8)	1002 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.074			0.039
0	259 (75.1)	822 (72.9)		186 (74.4)	822 (72.9)	
1	43 (12.5)	143 (12.7)		30 (12.0)	143 (12.7)	
2	15 (4.3)	47 (4.2)		9 (3.6)	47 (4.2)	
3	28 (8.1)	115 (10.2)		25 (10.0)	115 (10.2)	
FRUIT_UNITS_T7, mean (SD)	1.72 (1.33)	1.97 (1.72)	0.165	1.74 (1.38)	1.97 (1.72)	0.150
RED_MEAT_T7, n (%)			0.079			0.089
1	24 (7.0)	72 (6.4)		14 (5.6)	72 (6.4)	
2	80 (23.2)	254 (22.5)		58 (23.2)	254 (22.5)	
3	212 (61.4)	721 (64.0)		155 (62.0)	721 (64.0)	
4	26 (7.5)	67 (5.9)		20 (8.0)	67 (5.9)	
5	3 (0.9)	13 (1.2)		3 (1.2)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.091			0.029
1	5 (1.4)	14 (1.2)		3 (1.2)	14 (1.2)	
2	16 (4.6)	43 (3.8)		10 (4.0)	43 (3.8)	
3	66 (19.1)	254 (22.5)		55 (22.0)	254 (22.5)	
4	99 (28.7)	316 (28.0)		68 (27.2)	316 (28.0)	
5	159 (46.1)	500 (44.4)		114 (45.6)	500 (44.4)	
LEAN_FISH_T7, n (%)			0.225			0.181
1	22 (6.4)	26 (2.3)		11 (4.4)	26 (2.3)	
2	52 (15.1)	153 (13.6)		43 (17.2)	153 (13.6)	
3	224 (64.9)	799 (70.9)		161 (64.4)	799 (70.9)	
4	40 (11.6)	136 (12.1)		30 (12.0)	136 (12.1)	

5	7 (2.0)	13 (1.2)		5 (2.0)	13 (1.2)	
FAT_FISH_T7, n (%)			0.163			0.125
1	52 (15.1)	114 (10.1)		33 (13.2)	114 (10.1)	
2	115 (33.3)	388 (34.4)		85 (34.0)	388 (34.4)	
3	158 (45.8)	553 (49.1)		120 (48.0)	553 (49.1)	
4	13 (3.8)	55 (4.9)		8 (3.2)	55 (4.9)	
5	7 (2.0)	17 (1.5)		4 (1.6)	17 (1.5)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.085			0.105
1	84 (24.3)	242 (21.5)		60 (24.0)	242 (21.5)	
2	175 (50.7)	610 (54.1)		123 (49.2)	610 (54.1)	
3	76 (22.0)	249 (22.1)		62 (24.8)	249 (22.1)	
4	10 (2.9)	26 (2.3)		5 (2.0)	26 (2.3)	
EXERCISE_T7, n (%)			0.182			0.121
1	45 (13.0)	101 (9.0)		25 (10.0)	101 (9.0)	
2	54 (15.7)	146 (13.0)		40 (16.0)	146 (13.0)	
3	51 (14.8)	155 (13.8)		38 (15.2)	155 (13.8)	
4	112 (32.5)	436 (38.7)		86 (34.4)	436 (38.7)	
5	83 (24.1)	289 (25.6)		61 (24.4)	289 (25.6)	
Dataset 8						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		251	1127	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.80 (12.91)	69.41 (9.72)	0.141
SEX_T7, n (%)			0.390			0.252
1	193 (55.9)	836 (74.2)		157 (62.5)	836 (74.2)	
BMI, mean (SD)	28.28 (4.95)	28.40 (4.35)	0.027	28.51 (5.00)	28.40 (4.35)	0.024
HEART_FAILURE_T7, n (%)			0.191			0.118
0	281 (81.4)	838 (74.4)		197 (78.5)	838 (74.4)	
1	31 (9.0)	114 (10.1)		25 (10.0)	114 (10.1)	
2	33 (9.6)	175 (15.5)		29 (11.6)	175 (15.5)	
ATRIAL_FIBRILLATION_T7, n (%)			0.155			0.114
0	233 (67.5)	837 (74.3)		176 (70.1)	837 (74.3)	
1	68 (19.7)	164 (14.6)		47 (18.7)	164 (14.6)	
2	44 (12.8)	126 (11.2)		28 (11.2)	126 (11.2)	
STROKE_T7, n (%)			0.045			0.024
2	44 (12.8)	161 (14.3)		38 (15.1)	161 (14.3)	
KIDNEY_DISEASE_T7, n (%)			0.129			0.127
0	283 (82.0)	976 (86.6)		206 (82.1)	976 (86.6)	
1	36 (10.4)	93 (8.3)		29 (11.6)	93 (8.3)	
2	26 (7.5)	58 (5.1)		16 (6.4)	58 (5.1)	
CANCER_T7, n (%)			0.072			0.079
0	278 (80.6)	921 (81.7)		200 (79.7)	921 (81.7)	

1	32 (9.3)	83 (7.4)		24 (9.6)	83 (7.4)	
2	35 (10.1)	123 (10.9)		27 (10.8)	123 (10.9)	
DIABETES_impu_new, n (%)			0.056			0.048
0	275 (79.7)	889 (78.9)		197 (78.5)	889 (78.9)	
1	58 (16.8)	207 (18.4)		45 (17.9)	207 (18.4)	
2	12 (3.5)	31 (2.8)		9 (3.6)	31 (2.8)	
Cons_GP_Times_impu, mean (SD)	4.34 (6.24)	4.12 (4.59)	0.040	4.48 (6.87)	4.12 (4.59)	0.061
Cons_Emergency_Times_impu, mean (SD)	0.41 (0.84)	0.30 (0.72)	0.148	0.41 (0.79)	0.30 (0.72)	0.152
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.29)	0.43 (0.90)	0.033	0.52 (1.42)	0.43 (0.90)	0.077
Cons_Specialist_Times_impu, mean (SD)	0.63 (1.82)	0.48 (2.57)	0.067	0.65 (1.91)	0.48 (2.57)	0.072
Cons_Clinic_Times_impu, mean (SD)	1.14 (2.55)	1.19 (4.79)	0.013	1.23 (2.70)	1.19 (4.79)	0.008
Alcohol_frequency_impu, n (%)			0.150			0.108
1	34 (9.9)	121 (10.7)		26 (10.4)	121 (10.7)	
2	85 (24.6)	209 (18.5)		57 (22.7)	209 (18.5)	
3	129 (37.4)	462 (41.0)		98 (39.0)	462 (41.0)	
4	69 (20.0)	243 (21.6)		49 (19.5)	243 (21.6)	
5	28 (8.1)	92 (8.2)		21 (8.4)	92 (8.2)	
Alcohol_units_impu, n (%)			0.075			0.095
0	36 (10.4)	119 (10.6)		25 (10.0)	119 (10.6)	
1	176 (51.0)	540 (47.9)		132 (52.6)	540 (47.9)	
2	101 (29.3)	367 (32.6)		74 (29.5)	367 (32.6)	
3	32 (9.3)	101 (9.0)		20 (8.0)	101 (9.0)	
Alcohol_units_6_impu, n (%)			0.104			0.083
1	190 (55.1)	663 (58.8)		142 (56.6)	663 (58.8)	
2	119 (34.5)	364 (32.3)		84 (33.5)	364 (32.3)	
3	27 (7.8)	74 (6.6)		19 (7.6)	74 (6.6)	
4	6 (1.7)	22 (2.0)		4 (1.6)	22 (2.0)	
5	3 (0.9)	4 (0.4)		2 (0.8)	4 (0.4)	
Smoke_impu, n (%)			0.305			0.170
1	57 (16.5)	139 (12.3)		41 (16.3)	139 (12.3)	
2	12 (3.5)	19 (1.7)		5 (2.0)	19 (1.7)	
3	167 (48.4)	711 (63.1)		138 (55.0)	711 (63.1)	
4	109 (31.6)	258 (22.9)		67 (26.7)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.054			0.073
1	22 (6.4)	67 (5.9)		17 (6.8)	67 (5.9)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	57 (5.1)		12 (4.8)	57 (5.1)	
4	303 (87.8)	1002 (88.9)		221 (88.0)	1002 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.101			0.087
0	261 (75.7)	821 (72.8)		190 (75.7)	821 (72.8)	
1	44 (12.8)	143 (12.7)		32 (12.7)	143 (12.7)	

2	14 (4.1)	46 (4.1)		8 (3.2)	46 (4.1)	
3	26 (7.5)	117 (10.4)		21 (8.4)	117 (10.4)	
FRUIT_UNITS_T7, mean (SD)	1.71 (1.33)	1.97 (1.72)	0.168	1.69 (1.35)	1.97 (1.72)	0.181
RED_MEAT_T7, n (%)			0.043			0.046
1	23 (6.7)	70 (6.2)		16 (6.4)	70 (6.2)	
2	79 (22.9)	255 (22.6)		58 (23.1)	255 (22.6)	
3	215 (62.3)	719 (63.8)		156 (62.2)	719 (63.8)	
4	24 (7.0)	69 (6.1)		17 (6.8)	69 (6.1)	
5	4 (1.2)	14 (1.2)		4 (1.6)	14 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.107			0.069
1	4 (1.2)	13 (1.2)		3 (1.2)	13 (1.2)	
2	17 (4.9)	44 (3.9)		12 (4.8)	44 (3.9)	
3	65 (18.8)	257 (22.8)		54 (21.5)	257 (22.8)	
4	102 (29.6)	313 (27.8)		75 (29.9)	313 (27.8)	
5	157 (45.5)	500 (44.4)		107 (42.6)	500 (44.4)	
LEAN_FISH_T7, n (%)			0.225			0.074
1	23 (6.7)	26 (2.3)		8 (3.2)	26 (2.3)	
2	53 (15.4)	152 (13.5)		37 (14.7)	152 (13.5)	
3	227 (65.8)	803 (71.3)		176 (70.1)	803 (71.3)	
4	38 (11.0)	134 (11.9)		27 (10.8)	134 (11.9)	
5	4 (1.2)	12 (1.1)		3 (1.2)	12 (1.1)	
FAT_FISH_T7, n (%)			0.175			0.125
1	54 (15.7)	115 (10.2)		31 (12.4)	115 (10.2)	
2	116 (33.6)	387 (34.3)		85 (33.9)	387 (34.3)	
3	155 (44.9)	552 (49.0)		124 (49.4)	552 (49.0)	
4	13 (3.8)	55 (4.9)		7 (2.8)	55 (4.9)	
5	7 (2.0)	18 (1.6)		4 (1.6)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.080			0.061
1	79 (22.9)	241 (21.4)		56 (22.3)	241 (21.4)	
2	179 (51.9)	617 (54.7)		130 (51.8)	617 (54.7)	
3	77 (22.3)	247 (21.9)		60 (23.9)	247 (21.9)	
4	10 (2.9)	22 (2.0)		5 (2.0)	22 (2.0)	
EXERCISE_T7, n (%)			0.169			0.168
1	43 (12.5)	106 (9.4)		32 (12.7)	106 (9.4)	
2	55 (15.9)	142 (12.6)		38 (15.1)	142 (12.6)	
3	51 (14.8)	157 (13.9)		40 (15.9)	157 (13.9)	
4	111 (32.2)	433 (38.4)		86 (34.3)	433 (38.4)	
5	85 (24.6)	289 (25.6)		55 (21.9)	289 (25.6)	
Dataset 9						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		259	1126	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.54 (12.90)	69.40 (9.72)	0.163
SEX_T7, n (%)			0.390			0.237

1	193 (55.9)	836 (74.2)		164 (63.3)	836 (74.2)	
BMI, mean (SD)	28.25 (4.96)	28.41 (4.36)	0.034	28.66 (4.84)	28.41 (4.36)	0.054
HEART_FAILURE_T7, n (%)			0.172			0.155
0	279 (80.9)	841 (74.6)		206 (79.5)	840 (74.6)	
1	30 (8.7)	105 (9.3)		25 (9.7)	105 (9.3)	
2	36 (10.4)	181 (16.1)		28 (10.8)	181 (16.1)	
ATRIAL_FIBRILLATION_T7, n (%)			0.133			0.100
0	237 (68.7)	841 (74.6)		182 (70.3)	841 (74.7)	
1	62 (18.0)	159 (14.1)		42 (16.2)	158 (14.0)	
2	46 (13.3)	127 (11.3)		35 (13.5)	127 (11.3)	
STROKE_T7, n (%)			0.054			0.046
2	43 (12.5)	161 (14.3)		33 (12.7)	161 (14.3)	
KIDNEY_DISEASE_T7, n (%)			0.141			0.131
0	281 (81.4)	975 (86.5)		212 (81.9)	975 (86.6)	
1	39 (11.3)	88 (7.8)		28 (10.8)	87 (7.7)	
2	25 (7.2)	64 (5.7)		19 (7.3)	64 (5.7)	
CANCER_T7, n (%)			0.024			0.038
0	279 (80.9)	921 (81.7)		208 (80.3)	920 (81.7)	
1	27 (7.8)	82 (7.3)		21 (8.1)	82 (7.3)	
2	39 (11.3)	124 (11.0)		30 (11.6)	124 (11.0)	
DIABETES_impu_new, n (%)			0.124			0.100
0	275 (79.7)	886 (78.6)		205 (79.2)	885 (78.6)	
1	49 (14.2)	196 (17.4)		39 (15.1)	196 (17.4)	
2	21 (6.1)	45 (4.0)		15 (5.8)	45 (4.0)	
Cons_GP_Times_impu, mean (SD)	4.24 (5.14)	4.09 (4.47)	0.031	4.11 (5.06)	4.09 (4.47)	0.005
Cons_Emergency_Times_impu, mean (SD)	0.41 (0.85)	0.32 (0.77)	0.114	0.36 (0.77)	0.32 (0.77)	0.052
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.41)	0.43 (0.90)	0.039	0.42 (1.27)	0.42 (0.90)	0.003
Cons_Specialist_Times_impu, mean (SD)	0.60 (1.60)	0.46 (2.49)	0.067	0.57 (1.58)	0.46 (2.49)	0.052
Cons_Clinic_Times_impu, mean (SD)	1.00 (2.33)	1.24 (5.29)	0.059	0.99 (2.21)	1.25 (5.29)	0.062
Alcohol_frequency_impu, n (%)			0.152			0.141
1	34 (9.9)	121 (10.7)		26 (10.0)	121 (10.7)	
2	85 (24.6)	209 (18.5)		62 (23.9)	208 (18.5)	
3	128 (37.1)	462 (41.0)		100 (38.6)	462 (41.0)	
4	69 (20.0)	243 (21.6)		49 (18.9)	243 (21.6)	
5	29 (8.4)	92 (8.2)		22 (8.5)	92 (8.2)	
Alcohol_units_impu, n (%)			0.072			0.084
0	37 (10.7)	119 (10.6)		27 (10.4)	119 (10.6)	
1	175 (50.7)	542 (48.1)		127 (49.0)	541 (48.0)	
2	101 (29.3)	367 (32.6)		77 (29.7)	367 (32.6)	

3	32 (9.3)	99 (8.8)		28 (10.8)	99 (8.8)	
Alcohol_units_6_impu, n (%)			0.094			0.108
1	190 (55.1)	664 (58.9)		140 (54.1)	664 (59.0)	
2	120 (34.8)	364 (32.3)		91 (35.1)	363 (32.2)	
3	27 (7.8)	75 (6.7)		22 (8.5)	75 (6.7)	
4	6 (1.7)	21 (1.9)		5 (1.9)	21 (1.9)	
5	2 (0.6)	3 (0.3)		1 (0.4)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.190
1	57 (16.5)	139 (12.3)		42 (16.2)	139 (12.3)	
2	12 (3.5)	19 (1.7)		7 (2.7)	19 (1.7)	
3	167 (48.4)	711 (63.1)		140 (54.1)	710 (63.1)	
4	109 (31.6)	258 (22.9)		70 (27.0)	258 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.054			0.076
1	22 (6.4)	67 (5.9)		18 (6.9)	67 (6.0)	
2	1 (0.3)	1 (0.1)		1 (0.4)	1 (0.1)	
3	19 (5.5)	57 (5.1)		12 (4.6)	57 (5.1)	
4	303 (87.8)	1002 (88.9)		228 (88.0)	1001 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.113			0.138
0	262 (75.9)	818 (72.6)		193 (74.5)	817 (72.6)	
1	43 (12.5)	148 (13.1)		38 (14.7)	148 (13.1)	
2	15 (4.3)	45 (4.0)		11 (4.2)	45 (4.0)	
3	25 (7.2)	116 (10.3)		17 (6.6)	116 (10.3)	
FRUIT_UNITS_T7, mean (SD)	1.71 (1.34)	1.97 (1.72)	0.167	1.77 (1.42)	1.93 (1.29)	0.118
RED_MEAT_T7, n (%)			0.047			0.041
1	23 (6.7)	69 (6.1)		16 (6.2)	69 (6.1)	
2	77 (22.3)	254 (22.5)		55 (21.2)	254 (22.6)	
3	218 (63.2)	721 (64.0)		167 (64.5)	720 (63.9)	
4	24 (7.0)	70 (6.2)		18 (6.9)	70 (6.2)	
5	3 (0.9)	13 (1.2)		3 (1.2)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.108			0.084
1	4 (1.2)	12 (1.1)		3 (1.2)	12 (1.1)	
2	15 (4.3)	45 (4.0)		8 (3.1)	45 (4.0)	
3	64 (18.6)	258 (22.9)		53 (20.5)	258 (22.9)	
4	102 (29.6)	311 (27.6)		77 (29.7)	310 (27.5)	
5	160 (46.4)	501 (44.5)		118 (45.6)	501 (44.5)	
LEAN_FISH_T7, n (%)			0.225			0.155
1	23 (6.7)	27 (2.4)		12 (4.6)	27 (2.4)	
2	53 (15.4)	153 (13.6)		43 (16.6)	153 (13.6)	
3	224 (64.9)	801 (71.1)		174 (67.2)	800 (71.0)	
4	39 (11.3)	132 (11.7)		27 (10.4)	132 (11.7)	
5	6 (1.7)	14 (1.2)		3 (1.2)	14 (1.2)	
FAT_FISH_T7, n (%)			0.139			0.124
1	51 (14.8)	116 (10.3)		35 (13.5)	115 (10.2)	

2	116 (33.6)	390 (34.6)		87 (33.6)	390 (34.6)	
3	157 (45.5)	548 (48.6)		121 (46.7)	548 (48.7)	
4	15 (4.3)	55 (4.9)		10 (3.9)	55 (4.9)	
5	6 (1.7)	18 (1.6)		6 (2.3)	18 (1.6)	
PHYS_ACTIVITY_LEISURE_ T7, n (%)			0.096			0.081
1	83 (24.1)	229 (20.3)		61 (23.6)	228 (20.2)	
2	181 (52.5)	626 (55.5)		138 (53.3)	626 (55.6)	
3	72 (20.9)	247 (21.9)		55 (21.2)	247 (21.9)	
4	9 (2.6)	25 (2.2)		5 (1.9)	25 (2.2)	
EXERCISE_T7, n (%)			0.186			0.129
1	44 (12.8)	100 (8.9)		28 (10.8)	100 (8.9)	
2	55 (15.9)	144 (12.8)		41 (15.8)	144 (12.8)	
3	51 (14.8)	157 (13.9)		36 (13.9)	157 (13.9)	
4	111 (32.2)	437 (38.8)		88 (34.0)	436 (38.7)	
5	84 (24.3)	289 (25.6)		66 (25.5)	289 (25.7)	
Dataset 10						
	Before matching			**After matching**		
	Not LLD user	LLD user	SMD	Not LLD user	LLD user	SMD
n	345	1127		251	1124	
AGE, mean (SD)	66.34 (13.45)	69.41 (9.72)	0.261	67.57 (12.87)	69.39 (9.73)	0.160
SEX_T7, n (%)			0.390			0.294
1	193 (55.9)	836 (74.2)		152 (60.6)	834 (74.2)	
BMI, mean (SD)	28.17 (4.94)	28.41 (4.35)	0.050	28.37 (4.96)	28.39 (4.34)	0.005
HEART_FAILURE_T7, n (%)			0.204			0.158
0	283 (82.0)	832 (73.8)		202 (80.5)	831 (73.9)	
1	27 (7.8)	114 (10.1)		20 (8.0)	114 (10.1)	
2	35 (10.1)	181 (16.1)		29 (11.6)	179 (15.9)	
ATRIAL_FIBRILLATION_T7, n (%)			0.137			0.041
0	239 (69.3)	846 (75.1)		186 (74.1)	845 (75.2)	
1	63 (18.3)	155 (13.8)		38 (15.1)	154 (13.7)	
2	43 (12.5)	126 (11.2)		27 (10.8)	125 (11.1)	
STROKE_T7, n (%)			0.113			0.126
2	37 (10.7)	163 (14.5)		26 (10.4)	163 (14.5)	
KIDNEY_DISEASE_T7, n (%)			0.142			0.139
0	281 (81.4)	976 (86.6)		205 (81.7)	974 (86.7)	
1	37 (10.7)	90 (8.0)		26 (10.4)	89 (7.9)	
2	27 (7.8)	61 (5.4)		20 (8.0)	61 (5.4)	
CANCER_T7, n (%)			0.032			0.019
0	279 (80.9)	922 (81.8)		204 (81.3)	919 (81.8)	
1	25 (7.2)	73 (6.5)		16 (6.4)	73 (6.5)	
2	41 (11.9)	132 (11.7)		31 (12.4)	132 (11.7)	
DIABETES_impu_new, n (%)			0.070			0.101

0	281 (81.4)	893 (79.2)		208 (82.9)	892 (79.4)	
1	51 (14.8)	195 (17.3)		34 (13.5)	193 (17.2)	
2	13 (3.8)	39 (3.5)		9 (3.6)	39 (3.5)	
Cons_GP_Times_impu, mean (SD)	4.18 (5.12)	4.13 (4.51)	0.011	4.15 (5.28)	4.11 (4.49)	0.008
Cons_Emergency_Times_impu, mean (SD)	0.39 (0.94)	0.30 (0.72)	0.113	0.29 (0.65)	0.30 (0.72)	0.002
Cons_Hospital_Times_impu, mean (SD)	0.43 (1.26)	0.44 (0.91)	0.002	0.45 (1.39)	0.44 (0.91)	0.013
Cons_Specialist_Times_impu, mean (SD)	0.64 (1.80)	0.50 (2.59)	0.063	0.51 (1.38)	0.50 (2.60)	0.005
Cons_Clinic_Times_impu, mean (SD)	1.44 (5.05)	1.13 (4.25)	0.065	1.19 (3.01)	1.13 (4.26)	0.016
Alcohol_frequency_impu, n (%)			0.150			0.142
1	34 (9.9)	121 (10.7)		20 (8.0)	121 (10.8)	
2	85 (24.6)	209 (18.5)		58 (23.1)	208 (18.5)	
3	129 (37.4)	462 (41.0)		99 (39.4)	461 (41.0)	
4	69 (20.0)	243 (21.6)		52 (20.7)	243 (21.6)	
5	28 (8.1)	92 (8.2)		22 (8.8)	91 (8.1)	
Alcohol_units_impu, n (%)			0.075			0.096
0	36 (10.4)	120 (10.6)		21 (8.4)	120 (10.7)	
1	176 (51.0)	540 (47.9)		127 (50.6)	537 (47.8)	
2	101 (29.3)	367 (32.6)		78 (31.1)	367 (32.7)	
3	32 (9.3)	100 (8.9)		25 (10.0)	100 (8.9)	
Alcohol_units_6_impu, n (%)			0.098			0.083
1	191 (55.4)	664 (58.9)		139 (55.4)	663 (59.0)	
2	118 (34.2)	363 (32.2)		86 (34.3)	361 (32.1)	
3	28 (8.1)	74 (6.6)		20 (8.0)	74 (6.6)	
4	6 (1.7)	23 (2.0)		5 (2.0)	23 (2.0)	
5	2 (0.6)	3 (0.3)		1 (0.4)	3 (0.3)	
Smoke_impu, n (%)			0.305			0.195
1	57 (16.5)	139 (12.3)		35 (13.9)	139 (12.4)	
2	12 (3.5)	19 (1.7)		8 (3.2)	19 (1.7)	
3	167 (48.4)	711 (63.1)		136 (54.2)	709 (63.1)	
4	109 (31.6)	258 (22.9)		72 (28.7)	257 (22.9)	
Snuff_chewing_tobacco_impu, n (%)			0.054			0.069
1	22 (6.4)	67 (5.9)		12 (4.8)	67 (6.0)	
2	1 (0.3)	1 (0.1)		0 (0.0)	1 (0.1)	
3	19 (5.5)	57 (5.1)		12 (4.8)	57 (5.1)	
4	303 (87.8)	1002 (88.9)		227 (90.4)	999 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.098			0.063
0	260 (75.4)	822 (72.9)		189 (75.3)	819 (72.9)	
1	44 (12.8)	144 (12.8)		30 (12.0)	144 (12.8)	
2	15 (4.3)	45 (4.0)		10 (4.0)	45 (4.0)	
3	26 (7.5)	116 (10.3)		22 (8.8)	116 (10.3)	

FRUIT_UNITS_T7, mean (SD)	1.75 (1.37)	1.97 (1.71)	0.141	1.81 (1.46)	1.92 (1.25)	0.080
RED_MEAT_T7, n (%)			0.089			
1	24 (7.0)	74 (6.6)		19 (7.6)	74 (6.6)	
2	75 (21.7)	256 (22.7)		54 (21.5)	256 (22.8)	
3	216 (62.6)	715 (63.4)		159 (63.3)	714 (63.5)	
4	27 (7.8)	67 (5.9)		17 (6.8)	67 (6.0)	
5	3 (0.9)	15 (1.3)		2 (0.8)	13 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.114			0.124
1	3 (0.9)	12 (1.1)		3 (1.2)	12 (1.1)	
2	18 (5.2)	47 (4.2)		12 (4.8)	47 (4.2)	
3	64 (18.6)	257 (22.8)		45 (17.9)	257 (22.9)	
4	100 (29.0)	310 (27.5)		73 (29.1)	309 (27.5)	
5	160 (46.4)	501 (44.5)		118 (47.0)	499 (44.4)	
LEAN_FISH_T7, n (%)			0.240			0.112
1	24 (7.0)	27 (2.4)		11 (4.4)	27 (2.4)	
2	52 (15.1)	153 (13.6)		34 (13.5)	153 (13.6)	
3	223 (64.6)	803 (71.3)		176 (70.1)	800 (71.2)	
4	40 (11.6)	133 (11.8)		28 (11.2)	133 (11.8)	
5	6 (1.7)	11 (1.0)		2 (0.8)	11 (1.0)	
FAT_FISH_T7, n (%)			0.159			0.103
1	50 (14.5)	115 (10.2)		33 (13.1)	114 (10.1)	
2	117 (33.9)	391 (34.7)		83 (33.1)	391 (34.8)	
3	155 (44.9)	551 (48.9)		119 (47.4)	549 (48.8)	
4	14 (4.1)	53 (4.7)		11 (4.4)	53 (4.7)	
5	9 (2.6)	17 (1.5)		5 (2.0)	17 (1.5)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.088			0.055
1	84 (24.3)	237 (21.0)		51 (20.3)	234 (20.8)	
2	178 (51.6)	622 (55.2)		137 (54.6)	622 (55.3)	
3	74 (21.4)	242 (21.5)		55 (21.9)	242 (21.5)	
4	9 (2.6)	26 (2.3)		8 (3.2)	26 (2.3)	
EXERCISE_T7, n (%)			0.176			0.157
1	44 (12.8)	105 (9.3)		30 (12.0)	105 (9.3)	
2	54 (15.7)	141 (12.5)		38 (15.1)	140 (12.5)	
3	52 (15.1)	158 (14.0)		33 (13.1)	158 (14.1)	
4	111 (32.2)	435 (38.6)		81 (32.3)	433 (38.5)	
5	84 (24.3)	288 (25.6)		69 (27.5)	288 (25.6)	

SMD, standardized mean difference

Supplementary table 6: Results from propensity score matching of the ten imputed datasets for the logistic regression analysis of the association between use of antihypertensive drugs and achieving the treatment goal for blood pressure among those with self-reported hypertension

Dataset 1						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		46	762	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	64.17 (11.06)	69.84 (9.81)	0.542
SEX_T7, n (%)			0.013			0.113
1	43 (67.2)	508 (66.6)		33 (71.7)	507 (66.5)	
BMI, mean (SD)	28.99 (5.07)	28.99 (4.54)	0.001	28.53 (4.76)	28.99 (4.55)	0.100
HEART_FAILURE_T7, n (%)			0.340			0.247
0	55 (85.9)	559 (73.3)		38 (82.6)	559 (73.4)	
1	2 (3.1)	72 (9.4)		2 (4.3)	72 (9.4)	
2	7 (10.9)	132 (17.3)		6 (13.0)	131 (17.2)	
ATRIAL_FIBRILLATION_T7, n (%)			0.216			0.239
0	40 (62.5)	544 (71.3)		30 (65.2)	544 (71.4)	
1	11 (17.2)	121 (15.9)		6 (13.0)	120 (15.7)	
2	13 (20.3)	98 (12.8)		10 (21.7)	98 (12.9)	
STROKE_T7, n (%)			0.135			0.002
2	8 (12.5)	132 (17.3)		8 (17.4)	132 (17.3)	
KIDNEY_DISEASE_T7, n (%)			0.235			0.229
0	53 (82.8)	654 (85.7)		38 (82.6)	653 (85.7)	
1	4 (6.2)	70 (9.2)		3 (6.5)	70 (9.2)	
2	7 (10.9)	39 (5.1)		5 (10.9)	39 (5.1)	
CANCER_T7, n (%)			0.205			0.193
0	56 (87.5)	620 (81.3)		40 (87.0)	619 (81.2)	
1	4 (6.2)	51 (6.7)		3 (6.5)	51 (6.7)	
2	4 (6.2)	92 (12.1)		3 (6.5)	92 (12.1)	
DIABETES_impu_new, n (%)			0.038			0.139
0	47 (73.4)	573 (75.1)		35 (76.1)	572 (75.1)	
1	13 (20.3)	145 (19.0)		7 (15.2)	145 (19.0)	
2	4 (6.2)	45 (5.9)		4 (8.7)	45 (5.9)	
Cons_GP_Times_impu, mean (SD)	3.66 (3.32)	5.11 (6.78)	0.271	3.61 (2.84)	5.11 (6.79)	0.288
Cons_Emergency_Times_impu, mean (SD)	0.33 (0.64)	0.34 (0.80)	0.023	0.26 (0.57)	0.35 (0.80)	0.121
Cons_Hospital_Times_impu, mean (SD)	0.50 (1.62)	0.47 (1.01)	0.024	0.28 (0.58)	0.47 (1.01)	0.226
Cons_Specialist_Times_impu, mean (SD)	0.48 (0.96)	0.56 (3.04)	0.035	0.54 (1.03)	0.56 (3.04)	0.009
Cons_Clinic_Times_impu, mean (SD)	0.73 (1.34)	1.20 (3.54)	0.174	0.93 (1.51)	1.20 (3.54)	0.098
Alcohol_frequency_impu, n (%)			0.160			0.283
1	7 (10.9)	79 (10.4)		2 (4.3)	79 (10.4)	
2	14 (21.9)	160 (21.0)		10 (21.7)	160 (21.0)	
3	26 (40.6)	285 (37.4)		18 (39.1)	284 (37.3)	
4	10 (15.6)	166 (21.8)		9 (19.6)	166 (21.8)	
5	7 (10.9)	73 (9.6)		7 (15.2)	73 (9.6)	
Alcohol_units_impu, n (%)			0.203			0.304

0	8 (12.5)	81 (10.6)		2 (4.3)	81 (10.6)	
1	28 (43.8)	372 (48.8)		23 (50.0)	372 (48.8)	
2	24 (37.5)	233 (30.5)		18 (39.1)	232 (30.4)	
3	4 (6.2)	77 (10.1)		3 (6.5)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.296			0.290
1	33 (51.6)	448 (58.7)		23 (50.0)	447 (58.7)	
2	27 (42.2)	237 (31.1)		20 (43.5)	237 (31.1)	
3	2 (3.1)	55 (7.2)		2 (4.3)	55 (7.2)	
4	1 (1.6)	18 (2.4)		1 (2.2)	18 (2.4)	
5	1 (1.6)	5 (0.7)		0 (0.0)	5 (0.7)	
Smoke_impu, n (%)			0.230			0.255
1	4 (6.2)	86 (11.3)		3 (6.5)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		29 (63.0)	464 (60.9)	
4	22 (34.4)	200 (26.2)		14 (30.4)	200 (26.2)	
Snuff_chewing_tobacco_impu, n (%)			0.098			0.072
1	5 (7.8)	44 (5.8)		3 (6.5)	43 (5.6)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		3 (6.5)	39 (5.1)	
4	55 (85.9)	680 (89.1)		40 (87.0)	680 (89.2)	
Cod_liver_oil_omega3_impu, n (%)			0.239			0.141
0	41 (64.1)	560 (73.4)		31 (67.4)	560 (73.5)	
1	11 (17.2)	101 (13.2)		8 (17.4)	101 (13.3)	
2	5 (7.8)	27 (3.5)		2 (4.3)	26 (3.4)	
3	7 (10.9)	75 (9.8)		5 (10.9)	75 (9.8)	
FRUIT_UNITS_T7, mean (SD)	1.81 (1.37)	2.06 (1.94)	0.144	2.04 (1.48)	2.05 (1.94)	0.005
RED_MEAT_T7, n (%)			0.438			0.399
1	9 (14.1)	42 (5.5)		7 (15.2)	42 (5.5)	
2	14 (21.9)	163 (21.4)		11 (23.9)	163 (21.4)	
3	32 (50.0)	510 (66.8)		25 (54.3)	509 (66.8)	
4	7 (10.9)	37 (4.8)		3 (6.5)	37 (4.9)	
5	2 (3.1)	11 (1.4)		0 (0.0)	11 (1.4)	
FRUITS_VEG_BERRY_T7, n (%)			0.253			0.201
1	0 (0.0)	8 (1.0)		0 (0.0)	8 (1.0)	
2	5 (7.8)	31 (4.1)		2 (4.3)	31 (4.1)	
3	12 (18.8)	151 (19.8)		8 (17.4)	151 (19.8)	
4	14 (21.9)	212 (27.8)		11 (23.9)	212 (27.8)	
5	33 (51.6)	361 (47.3)		25 (54.3)	360 (47.2)	
LEAN_FISH_T7, n (%)			0.406			0.299
1	7 (10.9)	20 (2.6)		3 (6.5)	20 (2.6)	
2	8 (12.5)	100 (13.1)		7 (15.2)	100 (13.1)	
3	43 (67.2)	531 (69.6)		32 (69.6)	530 (69.6)	
4	4 (6.2)	99 (13.0)		4 (8.7)	99 (13.0)	
5	2 (3.1)	13 (1.7)		0 (0.0)	13 (1.7)	
FAT_FISH_T7, n (%)			0.271			0.153
1	8 (12.5)	87 (11.4)		6 (13.0)	87 (11.4)	
2	26 (40.6)	261 (34.2)		18 (39.1)	260 (34.1)	
3	25 (39.1)	368 (48.2)		19 (41.3)	368 (48.3)	
4	2 (3.1)	36 (4.7)		2 (4.3)	36 (4.7)	
5	3 (4.7)	11 (1.4)		1 (2.2)	11 (1.4)	

PHYS_ACTIVITY_LEISURE_T7, n (%)			0.295			0.194
1	14 (21.9)	169 (22.1)		8 (17.4)	169 (22.2)	
2	37 (57.8)	409 (53.6)		27 (58.7)	409 (53.7)	
3	9 (14.1)	170 (22.3)		9 (19.6)	169 (22.2)	
4	4 (6.2)	15 (2.0)		2 (4.3)	15 (2.0)	
EXERCISE_T7, n (%)			0.217			0.443
1	6 (9.4)	88 (11.5)		1 (2.2)	88 (11.5)	
2	10 (15.6)	90 (11.8)		9 (19.6)	90 (11.8)	
3	11 (17.2)	123 (16.1)		6 (13.0)	123 (16.1)	
4	18 (28.1)	276 (36.2)		16 (34.8)	276 (36.2)	
5	19 (29.7)	186 (24.4)		14 (30.4)	185 (24.3)	
Dataset 2						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		48	762	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	65.77 (10.39)	69.84 (9.81)	0.402
SEX_T7, n (%)			0.013			0.041
1	43 (67.2)	508 (66.6)		31 (64.6)	507 (66.5)	
BMI, mean (SD)	28.99 (5.07)	28.99 (4.54)	0.001	28.83 (4.63)	28.99 (4.54)	0.035
HEART_FAILURE_T7, n (%)			0.389			0.356
0	54 (84.4)	563 (73.8)		40 (83.3)	562 (73.8)	
1	1 (1.6)	79 (10.4)		1 (2.1)	79 (10.4)	
2	9 (14.1)	121 (15.9)		7 (14.6)	121 (15.9)	
ATRIAL_FIBRILLATION_T7, n (%)			0.266			0.185
0	39 (60.9)	546 (71.6)		31 (64.6)	546 (71.7)	
1	11 (17.2)	122 (16.0)		8 (16.7)	122 (16.0)	
2	14 (21.9)	95 (12.5)		9 (18.8)	94 (12.3)	
STROKE_T7, n (%)			0.089			0.075
2	9 (14.1)	132 (17.3)		7 (14.6)	132 (17.3)	
KIDNEY_DISEASE_T7, n (%)			0.180			0.013
0	53 (82.8)	655 (85.8)		41 (85.4)	654 (85.8)	
1	4 (6.2)	61 (8.0)		4 (8.3)	61 (8.0)	
2	7 (10.9)	47 (6.2)		3 (6.2)	47 (6.2)	
CANCER_T7, n (%)			0.179			0.208
0	56 (87.5)	618 (81.0)		42 (87.5)	617 (81.0)	
1	3 (4.7)	53 (6.9)		3 (6.2)	53 (7.0)	
2	5 (7.8)	92 (12.1)		3 (6.2)	92 (12.1)	
DIABETES_impu_new, n (%)			0.075			0.027
0	47 (73.4)	575 (75.4)		36 (75.0)	574 (75.3)	
1	13 (20.3)	153 (20.1)		10 (20.8)	153 (20.1)	
2	4 (6.2)	35 (4.6)		2 (4.2)	35 (4.6)	
Cons_GP_Times_impu, mean (SD)	3.56 (3.00)	4.78 (5.61)	0.271	3.83 (3.11)	4.78 (5.62)	0.208
Cons_Emergency_Times_impu, mean (SD)	0.31 (0.59)	0.34 (0.79)	0.042	0.31 (0.59)	0.34 (0.79)	0.043
Cons_Hospital_Times_impu, mean (SD)	0.48 (1.61)	0.47 (1.01)	0.012	0.50 (1.77)	0.47 (1.01)	0.022
Cons_Specialist_Times_impu, mean (SD)	0.53 (0.98)	0.52 (2.94)	0.004	0.65 (1.08)	0.52 (2.94)	0.056

Cons_Clinic_Times_impu, mean (SD)	1.03 (2.30)	1.17 (3.51)	0.045	1.33 (2.58)	1.17 (3.51)	0.054
Alcohol_frequency_impu, n (%)			0.180			0.307
1	6 (9.4)	79 (10.4)		2 (4.2)	79 (10.4)	
2	14 (21.9)	160 (21.0)		10 (20.8)	160 (21.0)	
3	26 (40.6)	285 (37.4)		22 (45.8)	284 (37.3)	
4	10 (15.6)	166 (21.8)		8 (16.7)	166 (21.8)	
5	8 (12.5)	73 (9.6)		6 (12.5)	73 (9.6)	
Alcohol_units_impu, n (%)			0.214			0.283
0	7 (10.9)	81 (10.6)		3 (6.2)	81 (10.6)	
1	28 (43.8)	371 (48.6)		22 (45.8)	371 (48.7)	
2	25 (39.1)	233 (30.5)		20 (41.7)	232 (30.4)	
3	4 (6.2)	78 (10.2)		3 (6.2)	78 (10.2)	
Alcohol_units_6_impu, n (%)			0.296			0.391
1	34 (53.1)	449 (58.8)		27 (56.2)	449 (58.9)	
2	27 (42.2)	237 (31.1)		20 (41.7)	236 (31.0)	
3	2 (3.1)	55 (7.2)		1 (2.1)	55 (7.2)	
4	1 (1.6)	18 (2.4)		0 (0.0)	18 (2.4)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.243
1	4 (6.2)	86 (11.3)		4 (8.3)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		28 (58.3)	464 (60.9)	
4	22 (34.4)	200 (26.2)		16 (33.3)	200 (26.2)	
Snuff_chewing_tobacco_impu, n (%)			0.095			0.126
1	5 (7.8)	44 (5.8)		3 (6.2)	44 (5.8)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	40 (5.2)		4 (8.3)	40 (5.2)	
4	55 (85.9)	679 (89.0)		41 (85.4)	678 (89.0)	
Cod_liver_oil_omega3_impu, n (%)			0.221			0.155
0	41 (64.1)	557 (73.0)		33 (68.8)	557 (73.1)	
1	11 (17.2)	102 (13.4)		9 (18.8)	101 (13.3)	
2	5 (7.8)	30 (3.9)		2 (4.2)	30 (3.9)	
3	7 (10.9)	74 (9.7)		4 (8.3)	74 (9.7)	
FRUIT_UNITS_T7, mean (SD)	1.83 (1.44)	2.09 (1.97)	0.151	1.92 (1.57)	2.08 (1.96)	0.093
RED_MEAT_T7, n (%)			0.465			0.435
1	9 (14.1)	44 (5.8)		7 (14.6)	44 (5.8)	
2	15 (23.4)	166 (21.8)		15 (31.2)	166 (21.8)	
3	32 (50.0)	506 (66.3)		24 (50.0)	505 (66.3)	
4	8 (12.5)	38 (5.0)		2 (4.2)	38 (5.0)	
5	0 (0.0)	9 (1.2)		0 (0.0)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.206			0.205
1	0 (0.0)	8 (1.0)		0 (0.0)	8 (1.0)	
2	4 (6.2)	32 (4.2)		3 (6.2)	32 (4.2)	
3	12 (18.8)	152 (19.9)		10 (20.8)	152 (19.9)	
4	15 (23.4)	213 (27.9)		11 (22.9)	213 (28.0)	
5	33 (51.6)	358 (46.9)		24 (50.0)	357 (46.9)	
LEAN_FISH_T7, n (%)			0.396			0.255
1	7 (10.9)	21 (2.8)		3 (6.2)	20 (2.6)	
2	9 (14.1)	103 (13.5)		7 (14.6)	103 (13.5)	
3	43 (67.2)	531 (69.6)		33 (68.8)	531 (69.7)	

4	5 (7.8)	97 (12.7)		5 (10.4)	97 (12.7)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FAT_FISH_T7, n (%)			0.293			0.344
1	9 (14.1)	88 (11.5)		7 (14.6)	87 (11.4)	
2	28 (43.8)	261 (34.2)		22 (45.8)	261 (34.3)	
3	25 (39.1)	367 (48.1)		18 (37.5)	367 (48.2)	
4	1 (1.6)	38 (5.0)		1 (2.1)	38 (5.0)	
5	1 (1.6)	9 (1.2)		0 (0.0)	9 (1.2)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.279			0.163
1	14 (21.9)	176 (23.1)		12 (25.0)	176 (23.1)	
2	37 (57.8)	404 (52.9)		26 (54.2)	404 (53.0)	
3	9 (14.1)	166 (21.8)		8 (16.7)	165 (21.7)	
4	4 (6.2)	17 (2.2)		2 (4.2)	17 (2.2)	
EXERCISE_T7, n (%)			0.213			0.348
1	6 (9.4)	91 (11.9)		3 (6.2)	91 (11.9)	
2	10 (15.6)	92 (12.1)		10 (20.8)	92 (12.1)	
3	12 (18.8)	122 (16.0)		8 (16.7)	122 (16.0)	
4	18 (28.1)	274 (35.9)		13 (27.1)	274 (36.0)	
5	18 (28.1)	184 (24.1)		14 (29.2)	183 (24.0)	
Dataset 3						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		46	760	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	65.02 (11.05)	69.84 (9.82)	0.461
SEX_T7, n (%)			0.013			0.064
1	43 (67.2)	508 (66.6)		32 (69.6)	506 (66.6)	
BMI, mean (SD)	28.99 (5.07)	29.01 (4.55)	0.003	28.88 (4.63)	29.02 (4.55)	0.030
HEART_FAILURE_T7, n (%)			0.344			0.312
0	54 (84.4)	560 (73.4)		39 (84.8)	557 (73.3)	
1	2 (3.1)	87 (11.4)		2 (4.3)	87 (11.4)	
2	8 (12.5)	116 (15.2)		5 (10.9)	116 (15.3)	
ATRIAL_FIBRILLATION_T7, n (%)			0.228			0.263
0	40 (62.5)	541 (70.9)		29 (63.0)	540 (71.1)	
1	11 (17.2)	129 (16.9)		7 (15.2)	129 (17.0)	
2	13 (20.3)	93 (12.2)		10 (21.7)	91 (12.0)	
STROKE_T7, n (%)			0.093			0.124
2	9 (14.1)	133 (17.4)		6 (13.0)	133 (17.5)	
KIDNEY_DISEASE_T7, n (%)			0.169			0.061
0	53 (82.8)	654 (85.7)		39 (84.8)	651 (85.7)	
1	5 (7.8)	70 (9.2)		4 (8.7)	70 (9.2)	
2	6 (9.4)	39 (5.1)		3 (6.5)	39 (5.1)	
CANCER_T7, n (%)			0.177			0.307
0	56 (87.5)	619 (81.1)		42 (91.3)	616 (81.1)	
1	3 (4.7)	58 (7.6)		2 (4.3)	58 (7.6)	
2	5 (7.8)	86 (11.3)		2 (4.3)	86 (11.3)	
DIABETES_impu_new, n (%)			0.075			0.160
0	47 (73.4)	574 (75.2)		37 (80.4)	571 (75.1)	
1	13 (20.3)	154 (20.2)		8 (17.4)	154 (20.3)	
2	4 (6.2)	35 (4.6)		1 (2.2)	35 (4.6)	

Cons_GP_Times_impu, mean (SD)	4.86 (8.57)	4.91 (5.79)	0.007	5.52 (9.89)	4.91 (5.79)	0.076
Cons_Emergency_Times_impu, mean (SD)	0.34 (0.74)	0.34 (0.78)	0.009	0.35 (0.77)	0.34 (0.78)	0.012
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.61)	0.48 (1.01)	0.006	0.52 (1.83)	0.48 (1.02)	0.030
Cons_Specialist_Times_impu, mean (SD)	0.56 (1.18)	0.56 (3.11)	0.001	0.74 (1.34)	0.56 (3.12)	0.074
Cons_Clinic_Times_impu, mean (SD)	1.06 (2.35)	1.18 (3.60)	0.037	1.28 (2.67)	1.18 (3.61)	0.033
Alcohol_frequency_impu, n (%)			0.169			0.283
1	6 (9.4)	79 (10.4)		2 (4.3)	79 (10.4)	
2	15 (23.4)	160 (21.0)		11 (23.9)	159 (20.9)	
3	26 (40.6)	285 (37.4)		19 (41.3)	283 (37.2)	
4	10 (15.6)	166 (21.8)		8 (17.4)	166 (21.8)	
5	7 (10.9)	73 (9.6)		6 (13.0)	73 (9.6)	
Alcohol_units_impu, n (%)			0.203			0.142
0	8 (12.5)	81 (10.6)		4 (8.7)	80 (10.5)	
1	28 (43.8)	372 (48.8)		21 (45.7)	371 (48.8)	
2	24 (37.5)	233 (30.5)		17 (37.0)	232 (30.5)	
3	4 (6.2)	77 (10.1)		4 (8.7)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.297			0.317
1	34 (53.1)	448 (58.7)		25 (54.3)	446 (58.7)	
2	27 (42.2)	237 (31.1)		19 (41.3)	236 (31.1)	
3	2 (3.1)	55 (7.2)		1 (2.2)	55 (7.2)	
4	1 (1.6)	19 (2.5)		1 (2.2)	19 (2.5)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.213
1	4 (6.2)	86 (11.3)		4 (8.7)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		28 (60.9)	463 (60.9)	
4	22 (34.4)	200 (26.2)		14 (30.4)	199 (26.2)	
Snuff_chewing_tobacco_impu, n (%)			0.098			0.152
1	5 (7.8)	44 (5.8)		2 (4.3)	44 (5.8)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		4 (8.7)	39 (5.1)	
4	55 (85.9)	680 (89.1)		40 (87.0)	677 (89.1)	
Cod_liver_oil_omega3_impu, n (%)			0.168			0.251
0	42 (65.6)	559 (73.3)		31 (67.4)	558 (73.4)	
1	11 (17.2)	99 (13.0)		10 (21.7)	98 (12.9)	
2	3 (4.7)	30 (3.9)		1 (2.2)	30 (3.9)	
3	8 (12.5)	75 (9.8)		4 (8.7)	74 (9.7)	
FRUIT_UNITS_T7, mean (SD)	1.80 (1.38)	2.06 (1.94)	0.155	1.89 (1.51)	2.05 (1.94)	0.093
RED_MEAT_T7, n (%)			0.452			0.346
1	9 (14.1)	45 (5.9)		7 (15.2)	45 (5.9)	
2	14 (21.9)	162 (21.2)		10 (21.7)	162 (21.3)	
3	33 (51.6)	509 (66.7)		27 (58.7)	506 (66.6)	
4	8 (12.5)	38 (5.0)		2 (4.3)	38 (5.0)	
5	0 (0.0)	9 (1.2)		0 (0.0)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.221			0.220
1	0 (0.0)	8 (1.0)		0 (0.0)	8 (1.1)	

2	5 (7.8)	35 (4.6)		3 (6.5)	35 (4.6)	
3	12 (18.8)	151 (19.8)		10 (21.7)	151 (19.9)	
4	15 (23.4)	213 (27.9)		10 (21.7)	213 (28.0)	
5	32 (50.0)	356 (46.7)		23 (50.0)	353 (46.4)	
LEAN_FISH_T7, n (%)			0.411			0.212
1	7 (10.9)	19 (2.5)		1 (2.2)	18 (2.4)	
2	9 (14.1)	103 (13.5)		8 (17.4)	103 (13.6)	
3	43 (67.2)	532 (69.7)		32 (69.6)	530 (69.7)	
4	5 (7.8)	97 (12.7)		5 (10.9)	97 (12.8)	
5	0 (0.0)	12 (1.6)		0 (0.0)	12 (1.6)	
FAT_FISH_T7, n (%)			0.297			0.240
1	8 (12.5)	87 (11.4)		7 (15.2)	86 (11.3)	
2	29 (45.3)	261 (34.2)		18 (39.1)	259 (34.1)	
3	25 (39.1)	369 (48.4)		19 (41.3)	369 (48.6)	
4	1 (1.6)	37 (4.8)		1 (2.2)	37 (4.9)	
5	1 (1.6)	9 (1.2)		1 (2.2)	9 (1.2)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.291			0.168
1	14 (21.9)	178 (23.3)		11 (23.9)	178 (23.4)	
2	37 (57.8)	404 (52.9)		25 (54.3)	402 (52.9)	
3	9 (14.1)	166 (21.8)		8 (17.4)	165 (21.7)	
4	4 (6.2)	15 (2.0)		2 (4.3)	15 (2.0)	
EXERCISE_T7, n (%)			0.189			0.225
1	7 (10.9)	90 (11.8)		4 (8.7)	90 (11.8)	
2	10 (15.6)	91 (11.9)		9 (19.6)	91 (12.0)	
3	11 (17.2)	121 (15.9)		7 (15.2)	121 (15.9)	
4	18 (28.1)	274 (35.9)		15 (32.6)	274 (36.1)	
5	18 (28.1)	187 (24.5)		11 (23.9)	184 (24.2)	
Dataset 4						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		45	761	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	63.98 (10.44)	69.85 (9.80)	0.580
SEX_T7, n (%)			0.013			0.043
1	43 (67.2)	508 (66.6)		29 (64.4)	506 (66.5)	
BMI, mean (SD)	28.99 (5.07)	29.01 (4.55)	0.004	28.73 (4.66)	29.01 (4.54)	0.060
HEART_FAILURE_T7, n (%)			0.301			0.324
0	54 (84.4)	567 (74.3)		37 (82.2)	566 (74.4)	
1	2 (3.1)	74 (9.7)		1 (2.2)	74 (9.7)	
2	8 (12.5)	122 (16.0)		7 (15.6)	121 (15.9)	
ATRIAL_FIBRILLATION_T7, n (%)			0.248			0.221
0	39 (60.9)	545 (71.4)		30 (66.7)	545 (71.6)	
1	12 (18.8)	125 (16.4)		6 (13.3)	124 (16.3)	
2	13 (20.3)	93 (12.2)		9 (20.0)	92 (12.1)	
STROKE_T7, n (%)			0.086			0.041
2	9 (14.1)	131 (17.2)		7 (15.6)	130 (17.1)	
KIDNEY_DISEASE_T7, n (%)			0.230			0.040
0	53 (82.8)	653 (85.6)		39 (86.7)	651 (85.5)	
1	4 (6.2)	70 (9.2)		4 (8.9)	70 (9.2)	
2	7 (10.9)	40 (5.2)		2 (4.4)	40 (5.3)	

CANCER_T7, n (%)			0.205			0.187
0	56 (87.5)	620 (81.3)		39 (86.7)	619 (81.3)	
1	4 (6.2)	51 (6.7)		3 (6.7)	50 (6.6)	
2	4 (6.2)	92 (12.1)		3 (6.7)	92 (12.1)	
DIABETES_impu_new, n (%)			0.067			0.176
0	47 (73.4)	577 (75.6)		36 (80.0)	576 (75.7)	
1	13 (20.3)	149 (19.5)		6 (13.3)	148 (19.4)	
2	4 (6.2)	37 (4.8)		3 (6.7)	37 (4.9)	
Cons_GP_Times_impu, mean (SD)	3.72 (3.33)	4.95 (6.09)	0.250	3.91 (3.36)	4.94 (6.09)	0.208
Cons_Emergency_Times_impu, mean (SD)	0.30 (0.58)	0.33 (0.78)	0.045	0.24 (0.53)	0.33 (0.78)	0.127
Cons_Hospital_Times_impu, mean (SD)	0.48 (1.61)	0.45 (0.99)	0.024	0.47 (1.83)	0.45 (0.99)	0.009
Cons_Specialist_Times_impu, mean (SD)	0.47 (0.96)	0.57 (3.10)	0.044	0.51 (1.04)	0.57 (3.10)	0.026
Cons_Clinic_Times_impu, mean (SD)	0.83 (1.69)	1.16 (3.49)	0.121	1.07 (1.95)	1.15 (3.49)	0.030
Alcohol_frequency_impu, n (%)			0.169			0.240
1	6 (9.4)	79 (10.4)		3 (6.7)	79 (10.4)	
2	15 (23.4)	160 (21.0)		12 (26.7)	159 (20.9)	
3	26 (40.6)	285 (37.4)		19 (42.2)	285 (37.5)	
4	10 (15.6)	166 (21.8)		7 (15.6)	165 (21.7)	
5	7 (10.9)	73 (9.6)		4 (8.9)	73 (9.6)	
Alcohol_units_impu, n (%)			0.214			0.260
0	7 (10.9)	81 (10.6)		4 (8.9)	81 (10.6)	
1	28 (43.8)	371 (48.6)		19 (42.2)	371 (48.8)	
2	25 (39.1)	233 (30.5)		19 (42.2)	231 (30.4)	
3	4 (6.2)	78 (10.2)		3 (6.7)	78 (10.2)	
Alcohol_units_6_impu, n (%)			0.270			0.346
1	33 (51.6)	449 (58.8)		24 (53.3)	448 (58.9)	
2	27 (42.2)	235 (30.8)		19 (42.2)	234 (30.7)	
3	3 (4.7)	56 (7.3)		2 (4.4)	56 (7.4)	
4	1 (1.6)	19 (2.5)		0 (0.0)	19 (2.5)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.239
1	4 (6.2)	86 (11.3)		4 (8.9)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		26 (57.8)	464 (61.0)	
4	22 (34.4)	200 (26.2)		15 (33.3)	199 (26.1)	
Snuff_chewing_tobacco_impu, n (%)			0.095			0.077
1	5 (7.8)	44 (5.8)		3 (6.7)	44 (5.8)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	40 (5.2)		3 (6.7)	39 (5.1)	
4	55 (85.9)	679 (89.0)		39 (86.7)	678 (89.1)	
Cod_liver_oil_omega3_impu, n (%)			0.198			0.159
0	41 (64.1)	557 (73.0)		32 (71.1)	556 (73.1)	
1	11 (17.2)	102 (13.4)		8 (17.8)	102 (13.4)	
2	4 (6.2)	30 (3.9)		2 (4.4)	29 (3.8)	
3	8 (12.5)	74 (9.7)		3 (6.7)	74 (9.7)	
FRUIT_UNITS_T7, mean (SD)	1.77 (1.39)	2.08 (1.95)	0.187	1.89 (1.56)	2.08 (1.95)	0.111
RED_MEAT_T7, n (%)			0.411			0.275

1	9 (14.1)	43 (5.6)		4 (8.9)	42 (5.5)	
2	14 (21.9)	165 (21.6)		13 (28.9)	165 (21.7)	
3	33 (51.6)	510 (66.8)		26 (57.8)	509 (66.9)	
4	7 (10.9)	36 (4.7)		1 (2.2)	36 (4.7)	
5	1 (1.6)	9 (1.2)		1 (2.2)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.222			0.181
1	0 (0.0)	7 (0.9)		0 (0.0)	7 (0.9)	
2	5 (7.8)	33 (4.3)		3 (6.7)	33 (4.3)	
3	11 (17.2)	153 (20.1)		10 (22.2)	152 (20.0)	
4	16 (25.0)	214 (28.0)		12 (26.7)	213 (28.0)	
5	32 (50.0)	356 (46.7)		20 (44.4)	356 (46.8)	
LEAN_FISH_T7, n (%)			0.388			0.296
1	7 (10.9)	20 (2.6)		3 (6.7)	20 (2.6)	
2	9 (14.1)	100 (13.1)		8 (17.8)	99 (13.0)	
3	42 (65.6)	534 (70.0)		29 (64.4)	534 (70.2)	
4	6 (9.4)	98 (12.8)		5 (11.1)	97 (12.7)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FAT_FISH_T7, n (%)			0.288			0.304
1	9 (14.1)	88 (11.5)		8 (17.8)	88 (11.6)	
2	26 (40.6)	260 (34.1)		18 (40.0)	259 (34.0)	
3	26 (40.6)	369 (48.4)		17 (37.8)	369 (48.5)	
4	1 (1.6)	37 (4.8)		1 (2.2)	37 (4.9)	
5	2 (3.1)	9 (1.2)		1 (2.2)	8 (1.1)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.278			0.198
1	14 (21.9)	172 (22.5)		11 (24.4)	172 (22.6)	
2	37 (57.8)	404 (52.9)		25 (55.6)	402 (52.8)	
3	9 (14.1)	169 (22.1)		7 (15.6)	169 (22.2)	
4	4 (6.2)	18 (2.4)		2 (4.4)	18 (2.4)	
EXERCISE_T7, n (%)			0.217			0.382
1	6 (9.4)	92 (12.1)		2 (4.4)	92 (12.1)	
2	10 (15.6)	92 (12.1)		9 (20.0)	91 (12.0)	
3	11 (17.2)	122 (16.0)		6 (13.3)	122 (16.0)	
4	18 (28.1)	273 (35.8)		14 (31.1)	273 (35.9)	
5	19 (29.7)	184 (24.1)		14 (31.1)	183 (24.0)	
Dataset 5						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		47	760	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	64.17 (10.77)	69.86 (9.80)	0.553
SEX_T7, n (%)			0.013			0.010
1	43 (67.2)	508 (66.6)		31 (66.0)	505 (66.4)	
BMI, mean (SD)	28.99 (5.07)	29.00 (4.54)	0.002	29.05 (5.18)	29.00 (4.55)	0.012
HEART_FAILURE_T7, n (%)			0.263			0.228
0	54 (84.4)	563 (73.8)		39 (83.0)	561 (73.8)	
1	4 (6.2)	85 (11.1)		3 (6.4)	84 (11.1)	
2	6 (9.4)	115 (15.1)		5 (10.6)	115 (15.1)	
ATRIAL_FIBRILLATION_T7, n (%)			0.246			0.227
0	39 (60.9)	544 (71.3)		29 (61.7)	544 (71.6)	

1	12 (18.8)	126 (16.5)		9 (19.1)	124 (16.3)	
2	13 (20.3)	93 (12.2)		9 (19.1)	92 (12.1)	
STROKE_T7, n (%)			0.089			0.067
2	9 (14.1)	132 (17.3)		7 (14.9)	132 (17.4)	
KIDNEY_DISEASE_T7, n (%)			0.156			0.079
0	53 (82.8)	654 (85.7)		40 (85.1)	652 (85.8)	
1	5 (7.8)	68 (8.9)		5 (10.6)	67 (8.8)	
2	6 (9.4)	41 (5.4)		2 (4.3)	41 (5.4)	
CANCER_T7, n (%)			0.216			0.208
0	56 (87.5)	618 (81.0)		41 (87.2)	616 (81.1)	
1	4 (6.2)	50 (6.6)		3 (6.4)	50 (6.6)	
2	4 (6.2)	95 (12.5)		3 (6.4)	94 (12.4)	
DIABETES_impu_new, n (%)			0.045			0.028
0	47 (73.4)	575 (75.4)		36 (76.6)	574 (75.5)	
1	14 (21.9)	156 (20.4)		9 (19.1)	154 (20.3)	
2	3 (4.7)	32 (4.2)		2 (4.3)	32 (4.2)	
Cons_GP_Times_impu, mean (SD)	4.00 (4.38)	4.99 (6.15)	0.186	4.30 (4.80)	4.97 (6.13)	0.123
Cons_Emergency_Times_impu, mean (SD)	0.28 (0.58)	0.33 (0.78)	0.075	0.26 (0.53)	0.33 (0.78)	0.118
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.61)	0.46 (0.99)	0.006	0.43 (1.79)	0.46 (0.99)	0.024
Cons_Specialist_Times_impu, mean (SD)	0.55 (1.01)	0.53 (2.96)	0.009	0.62 (1.07)	0.53 (2.97)	0.040
Cons_Clinic_Times_impu, mean (SD)	1.11 (2.39)	1.20 (3.53)	0.028	1.32 (2.70)	1.19 (3.54)	0.040
Alcohol_frequency_impu, n (%)			0.180			0.309
1	6 (9.4)	79 (10.4)		2 (4.3)	79 (10.4)	
2	14 (21.9)	160 (21.0)		10 (21.3)	159 (20.9)	
3	26 (40.6)	285 (37.4)		20 (42.6)	283 (37.2)	
4	10 (15.6)	166 (21.8)		8 (17.0)	166 (21.8)	
5	8 (12.5)	73 (9.6)		7 (14.9)	73 (9.6)	
Alcohol_units_impu, n (%)			0.158			0.322
0	7 (10.9)	81 (10.6)		2 (4.3)	81 (10.7)	
1	28 (43.8)	371 (48.6)		21 (44.7)	370 (48.7)	
2	24 (37.5)	234 (30.7)		20 (42.6)	232 (30.5)	
3	5 (7.8)	77 (10.1)		4 (8.5)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.266			0.264
1	33 (51.6)	449 (58.8)		23 (48.9)	448 (58.9)	
2	27 (42.2)	236 (30.9)		20 (42.6)	234 (30.8)	
3	3 (4.7)	55 (7.2)		3 (6.4)	55 (7.2)	
4	1 (1.6)	19 (2.5)		1 (2.1)	19 (2.5)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.205
1	4 (6.2)	86 (11.3)		4 (8.5)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		30 (63.8)	463 (60.9)	
4	22 (34.4)	200 (26.2)		13 (27.7)	199 (26.2)	
Snuff_chewing_tobacco_impu, n (%)			0.093			0.117
1	5 (7.8)	45 (5.9)		4 (8.5)	45 (5.9)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		3 (6.4)	39 (5.1)	
4	55 (85.9)	679 (89.0)		40 (85.1)	676 (88.9)	

Cod_liver_oil_omega3_impu, n (%)			0.193			0.126
0	41 (64.1)	555 (72.7)		33 (70.2)	553 (72.8)	
1	11 (17.2)	103 (13.5)		7 (14.9)	102 (13.4)	
2	4 (6.2)	30 (3.9)		3 (6.4)	30 (3.9)	
3	8 (12.5)	75 (9.8)		4 (8.5)	75 (9.9)	
FRUIT_UNITS_T7, mean (SD)	1.84 (1.38)	2.10 (2.00)	0.147	2.02 (1.52)	2.09 (2.00)	0.041
RED_MEAT_T7, n (%)			0.437			0.200
1	10 (15.6)	44 (5.8)		4 (8.5)	43 (5.7)	
2	14 (21.9)	166 (21.8)		12 (25.5)	166 (21.8)	
3	32 (50.0)	506 (66.3)		27 (57.4)	505 (66.4)	
4	7 (10.9)	38 (5.0)		3 (6.4)	37 (4.9)	
5	1 (1.6)	9 (1.2)		1 (2.1)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.222			0.252
1	0 (0.0)	9 (1.2)		0 (0.0)	9 (1.2)	
2	4 (6.2)	29 (3.8)		4 (8.5)	29 (3.8)	
3	12 (18.8)	152 (19.9)		9 (19.1)	151 (19.9)	
4	15 (23.4)	214 (28.0)		12 (25.5)	214 (28.2)	
5	33 (51.6)	359 (47.1)		22 (46.8)	357 (47.0)	
LEAN_FISH_T7, n (%)			0.436			0.249
1	8 (12.5)	19 (2.5)		2 (4.3)	18 (2.4)	
2	9 (14.1)	101 (13.2)		6 (12.8)	100 (13.2)	
3	42 (65.6)	536 (70.2)		35 (74.5)	536 (70.5)	
4	4 (6.2)	97 (12.7)		3 (6.4)	97 (12.8)	
5	1 (1.6)	10 (1.3)		1 (2.1)	9 (1.2)	
FAT_FISH_T7, n (%)			0.307			0.360
1	9 (14.1)	86 (11.3)		7 (14.9)	84 (11.1)	
2	27 (42.2)	264 (34.6)		20 (42.6)	264 (34.7)	
3	25 (39.1)	370 (48.5)		17 (36.2)	370 (48.7)	
4	1 (1.6)	35 (4.6)		1 (2.1)	35 (4.6)	
5	2 (3.1)	8 (1.0)		2 (4.3)	7 (0.9)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.287			0.089
1	14 (21.9)	171 (22.4)		11 (23.4)	170 (22.4)	
2	37 (57.8)	401 (52.6)		26 (55.3)	400 (52.6)	
3	9 (14.1)	173 (22.7)		9 (19.1)	172 (22.6)	
4	4 (6.2)	18 (2.4)		1 (2.1)	18 (2.4)	
EXERCISE_T7, n (%)			0.253			0.319
1	5 (7.8)	90 (11.8)		3 (6.4)	89 (11.7)	
2	11 (17.2)	91 (11.9)		10 (21.3)	91 (12.0)	
3	12 (18.8)	122 (16.0)		6 (12.8)	122 (16.1)	
4	18 (28.1)	273 (35.8)		15 (31.9)	272 (35.8)	
5	18 (28.1)	187 (24.5)		13 (27.7)	186 (24.5)	
Dataset 6						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		49	759	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	65.08 (10.80)	69.88 (9.81)	0.465
SEX_T7, n (%)			0.013			0.058
1	43 (67.2)	508 (66.6)		34 (69.4)	506 (66.7)	

BMI, mean (SD)	28.99 (5.07)	29.00 (4.54)	0.002	28.60 (4.62)	29.00 (4.54)	0.087
HEART_FAILURE_T7, n (%)			0.353			0.291
0	55 (85.9)	557 (73.0)		41 (83.7)	553 (72.9)	
1	2 (3.1)	78 (10.2)		2 (4.1)	78 (10.3)	
2	7 (10.9)	128 (16.8)		6 (12.2)	128 (16.9)	
ATRIAL_FIBRILLATION_T7, n (%)			0.222			0.184
0	40 (62.5)	544 (71.3)		31 (63.3)	541 (71.3)	
1	11 (17.2)	123 (16.1)		9 (18.4)	122 (16.1)	
2	13 (20.3)	96 (12.6)		9 (18.4)	96 (12.6)	
STROKE_T7, n (%)			0.089			0.028
2	9 (14.1)	132 (17.3)		8 (16.3)	132 (17.4)	
KIDNEY_DISEASE_T7, n (%)			0.186			0.063
0	53 (82.8)	651 (85.3)		41 (83.7)	648 (85.4)	
1	5 (7.8)	75 (9.8)		5 (10.2)	75 (9.9)	
2	6 (9.4)	37 (4.8)		3 (6.1)	36 (4.7)	
CANCER_T7, n (%)			0.273			0.320
0	56 (87.5)	619 (81.1)		42 (85.7)	616 (81.2)	
1	5 (7.8)	51 (6.7)		5 (10.2)	50 (6.6)	
2	3 (4.7)	93 (12.2)		2 (4.1)	93 (12.3)	
DIABETES_impu_new, n (%)			0.069			0.065
0	47 (73.4)	575 (75.4)		37 (75.5)	571 (75.2)	
1	14 (21.9)	147 (19.3)		10 (20.4)	147 (19.4)	
2	3 (4.7)	41 (5.4)		2 (4.1)	41 (5.4)	
Cons_GP_Times_impu, mean (SD)	3.34 (2.84)	4.90 (5.80)	0.340	3.69 (2.99)	4.90 (5.82)	0.261
Cons_Emergency_Times_impu, mean (SD)	0.28 (0.55)	0.33 (0.78)	0.065	0.24 (0.48)	0.33 (0.78)	0.125
Cons_Hospital_Times_impu, mean (SD)	0.48 (1.61)	0.46 (1.00)	0.015	0.47 (1.76)	0.47 (1.00)	0.003
Cons_Specialist_Times_impu, mean (SD)	0.53 (1.01)	0.64 (3.24)	0.045	0.61 (1.06)	0.64 (3.25)	0.011
Cons_Clinic_Times_impu, mean (SD)	0.69 (1.23)	1.16 (3.50)	0.181	0.80 (1.35)	1.16 (3.51)	0.138
Alcohol_frequency_impu, n (%)			0.169			0.227
1	6 (9.4)	79 (10.4)		3 (6.1)	79 (10.4)	
2	15 (23.4)	160 (21.0)		11 (22.4)	160 (21.1)	
3	26 (40.6)	285 (37.4)		21 (42.9)	284 (37.4)	
4	10 (15.6)	166 (21.8)		8 (16.3)	163 (21.5)	
5	7 (10.9)	73 (9.6)		6 (12.2)	73 (9.6)	
Alcohol_units_impu, n (%)			0.187			0.281
0	7 (10.9)	82 (10.7)		3 (6.1)	82 (10.8)	
1	29 (45.3)	371 (48.6)		23 (46.9)	370 (48.7)	
2	24 (37.5)	233 (30.5)		20 (40.8)	230 (30.3)	
3	4 (6.2)	77 (10.1)		3 (6.1)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.302			0.287
1	34 (53.1)	448 (58.7)		25 (51.0)	446 (58.8)	
2	27 (42.2)	236 (30.9)		21 (42.9)	234 (30.8)	
3	2 (3.1)	56 (7.3)		2 (4.1)	56 (7.4)	
4	1 (1.6)	19 (2.5)		1 (2.0)	19 (2.5)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.223
1	4 (6.2)	86 (11.3)		4 (8.2)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	

3	37 (57.8)	465 (60.9)		30 (61.2)	463 (61.0)	
4	22 (34.4)	200 (26.2)		15 (30.6)	198 (26.1)	
Snuff_chewing_tobacco_impu, n (%)			0.092			0.038
1	5 (7.8)	44 (5.8)		3 (6.1)	43 (5.7)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	41 (5.4)		3 (6.1)	41 (5.4)	
4	55 (85.9)	678 (88.9)		43 (87.8)	675 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.193			0.148
0	41 (64.1)	556 (72.9)		33 (67.3)	554 (73.0)	
1	11 (17.2)	101 (13.2)		9 (18.4)	100 (13.2)	
2	4 (6.2)	32 (4.2)		2 (4.1)	31 (4.1)	
3	8 (12.5)	74 (9.7)		5 (10.2)	74 (9.7)	
FRUIT_UNITS_T7, mean (SD)	1.81 (1.37)	2.06 (1.94)	0.148	1.92 (1.48)	2.06 (1.94)	0.081
RED_MEAT_T7, n (%)			0.503			0.377
1	11 (17.2)	43 (5.6)		7 (14.3)	41 (5.4)	
2	14 (21.9)	163 (21.4)		12 (24.5)	163 (21.5)	
3	32 (50.0)	508 (66.6)		27 (55.1)	506 (66.7)	
4	7 (10.9)	38 (5.0)		3 (6.1)	38 (5.0)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FRUITS_VEG_BERRY_T7, n (%)			0.187			0.171
1	0 (0.0)	7 (0.9)		0 (0.0)	7 (0.9)	
2	4 (6.2)	30 (3.9)		3 (6.1)	30 (4.0)	
3	12 (18.8)	152 (19.9)		10 (20.4)	151 (19.9)	
4	16 (25.0)	214 (28.0)		14 (28.6)	213 (28.1)	
5	32 (50.0)	360 (47.2)		22 (44.9)	358 (47.2)	
LEAN_FISH_T7, n (%)			0.438			0.287
1	8 (12.5)	20 (2.6)		3 (6.1)	19 (2.5)	
2	8 (12.5)	100 (13.1)		6 (12.2)	100 (13.2)	
3	43 (67.2)	535 (70.1)		36 (73.5)	533 (70.2)	
4	5 (7.8)	97 (12.7)		4 (8.2)	96 (12.6)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FAT_FISH_T7, n (%)			0.336			0.344
1	8 (12.5)	84 (11.0)		7 (14.3)	83 (10.9)	
2	29 (45.3)	260 (34.1)		21 (42.9)	259 (34.1)	
3	24 (37.5)	370 (48.5)		18 (36.7)	369 (48.6)	
4	1 (1.6)	38 (5.0)		1 (2.0)	38 (5.0)	
5	2 (3.1)	11 (1.4)		2 (4.1)	10 (1.3)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.275			0.131
1	14 (21.9)	169 (22.1)		11 (22.4)	168 (22.1)	
2	37 (57.8)	399 (52.3)		27 (55.1)	398 (52.4)	
3	9 (14.1)	174 (22.8)		9 (18.4)	173 (22.8)	
4	4 (6.2)	21 (2.8)		2 (4.1)	20 (2.6)	
EXERCISE_T7, n (%)			0.219			0.307
1	6 (9.4)	91 (11.9)		3 (6.1)	91 (12.0)	
2	10 (15.6)	90 (11.8)		10 (20.4)	89 (11.7)	
3	12 (18.8)	120 (15.7)		7 (14.3)	120 (15.8)	
4	18 (28.1)	276 (36.2)		16 (32.7)	275 (36.2)	
5	18 (28.1)	186 (24.4)		13 (26.5)	184 (24.2)	
Dataset 7						
	Before matching			**After matching**		

	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		47	760	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	64.21 (11.06)	69.85 (9.81)	0.539
SEX_T7, n (%)			0.013			0.013
1	43 (67.2)	508 (66.6)		31 (66.0)	506 (66.6)	
BMI, mean (SD)	28.99 (5.07)	28.99 (4.54)	0.001	28.64 (4.58)	28.99 (4.54)	0.077
HEART_FAILURE_T7, n (%)			0.313			0.259
0	54 (84.4)	564 (73.9)		39 (83.0)	561 (73.8)	
1	2 (3.1)	77 (10.1)		2 (4.3)	77 (10.1)	
2	8 (12.5)	122 (16.0)		6 (12.8)	122 (16.1)	
ATRIAL_FIBRILLATION_T7, n (%)			0.236			0.179
0	39 (60.9)	544 (71.3)		31 (66.0)	543 (71.4)	
1	12 (18.8)	121 (15.9)		7 (14.9)	121 (15.9)	
2	13 (20.3)	98 (12.8)		9 (19.1)	96 (12.6)	
STROKE_T7, n (%)			0.187			0.129
2	7 (10.9)	133 (17.4)		6 (12.8)	132 (17.4)	
KIDNEY_DISEASE_T7, n (%)			0.151			0.062
0	53 (82.8)	652 (85.5)		41 (87.2)	650 (85.5)	
1	5 (7.8)	69 (9.0)		4 (8.5)	68 (8.9)	
2	6 (9.4)	42 (5.5)		2 (4.3)	42 (5.5)	
CANCER_T7, n (%)			0.179			0.222
0	56 (87.5)	620 (81.3)		41 (87.2)	617 (81.2)	
1	3 (4.7)	45 (5.9)		3 (6.4)	45 (5.9)	
2	5 (7.8)	98 (12.8)		3 (6.4)	98 (12.9)	
DIABETES_impu_new, n (%)			0.051			0.079
0	47 (73.4)	575 (75.4)		37 (78.7)	573 (75.4)	
1	14 (21.9)	151 (19.8)		8 (17.0)	150 (19.7)	
2	3 (4.7)	37 (4.8)		2 (4.3)	37 (4.9)	
Cons_GP_Times_impu, mean (SD)	4.00 (4.50)	4.92 (5.50)	0.182	4.43 (4.97)	4.92 (5.51)	0.094
Cons_Emergency_Times_impu, mean (SD)	0.36 (0.70)	0.34 (0.78)	0.025	0.32 (0.66)	0.34 (0.79)	0.032
Cons_Hospital_Times_impu, mean (SD)	0.48 (1.61)	0.47 (1.01)	0.014	0.45 (1.78)	0.47 (1.01)	0.014
Cons_Specialist_Times_impu, mean (SD)	0.56 (1.18)	0.54 (2.96)	0.010	0.64 (1.29)	0.54 (2.96)	0.043
Cons_Clinic_Times_impu, mean (SD)	0.83 (1.53)	1.19 (3.56)	0.132	1.02 (1.71)	1.19 (3.57)	0.061
Alcohol_frequency_impu, n (%)			0.171			0.232
1	6 (9.4)	79 (10.4)		3 (6.4)	79 (10.4)	
2	14 (21.9)	160 (21.0)		8 (17.0)	159 (20.9)	
3	27 (42.2)	285 (37.4)		22 (46.8)	284 (37.4)	
4	10 (15.6)	166 (21.8)		9 (19.1)	166 (21.8)	
5	7 (10.9)	73 (9.6)		5 (10.6)	72 (9.5)	
Alcohol_units_impu, n (%)			0.160			0.244
0	7 (10.9)	81 (10.6)		3 (6.4)	81 (10.7)	
1	28 (43.8)	372 (48.8)		20 (42.6)	371 (48.8)	
2	24 (37.5)	233 (30.5)		19 (40.4)	231 (30.4)	
3	5 (7.8)	77 (10.1)		5 (10.6)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.274			0.270

1	33 (51.6)	448 (58.7)		27 (57.4)	447 (58.8)	
2	27 (42.2)	235 (30.8)		17 (36.2)	233 (30.7)	
3	3 (4.7)	57 (7.5)		3 (6.4)	57 (7.5)	
4	1 (1.6)	18 (2.4)		0 (0.0)	18 (2.4)	
5	0 (0.0)	5 (0.7)		0 (0.0)	5 (0.7)	
Smoke_impu, n (%)			0.230			0.249
1	4 (6.2)	86 (11.3)		4 (8.5)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		27 (57.4)	462 (60.8)	
4	22 (34.4)	200 (26.2)		16 (34.0)	200 (26.3)	
Snuff_chewing_tobacco_impu, n (%)			0.098			0.086
1	5 (7.8)	44 (5.8)		2 (4.3)	44 (5.8)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		3 (6.4)	39 (5.1)	
4	55 (85.9)	680 (89.1)		42 (89.4)	677 (89.1)	
Cod_liver_oil_omega3_impu, n (%)			0.210			0.175
0	41 (64.1)	557 (73.0)		31 (66.0)	555 (73.0)	
1	12 (18.8)	101 (13.2)		9 (19.1)	100 (13.2)	
2	4 (6.2)	29 (3.8)		2 (4.3)	29 (3.8)	
3	7 (10.9)	76 (10.0)		5 (10.6)	76 (10.0)	
FRUIT_UNITS_T7, mean (SD)	1.80 (1.42)	2.07 (1.95)	0.161	1.98 (1.52)	2.06 (1.95)	0.049
RED_MEAT_T7, n (%)			0.443			0.345
1	10 (15.6)	43 (5.6)		7 (14.9)	42 (5.5)	
2	14 (21.9)	165 (21.6)		11 (23.4)	164 (21.6)	
3	32 (50.0)	508 (66.6)		26 (55.3)	507 (66.7)	
4	7 (10.9)	38 (5.0)		2 (4.3)	38 (5.0)	
5	1 (1.6)	9 (1.2)		1 (2.1)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.233			0.266
1	0 (0.0)	8 (1.0)		0 (0.0)	8 (1.1)	
2	4 (6.2)	31 (4.1)		2 (4.3)	30 (3.9)	
3	12 (18.8)	153 (20.1)		10 (21.3)	153 (20.1)	
4	14 (21.9)	213 (27.9)		9 (19.1)	213 (28.0)	
5	34 (53.1)	358 (46.9)		26 (55.3)	356 (46.8)	
LEAN_FISH_T7, n (%)			0.434			0.353
1	8 (12.5)	19 (2.5)		3 (6.4)	16 (2.1)	
2	9 (14.1)	100 (13.1)		9 (19.1)	100 (13.2)	
3	42 (65.6)	534 (70.0)		31 (66.0)	534 (70.3)	
4	4 (6.2)	96 (12.6)		4 (8.5)	96 (12.6)	
5	1 (1.6)	14 (1.8)		0 (0.0)	14 (1.8)	
FAT_FISH_T7, n (%)			0.328			0.249
1	8 (12.5)	85 (11.1)		7 (14.9)	84 (11.1)	
2	27 (42.2)	260 (34.1)		19 (40.4)	259 (34.1)	
3	25 (39.1)	368 (48.2)		19 (40.4)	367 (48.3)	
4	1 (1.6)	38 (5.0)		1 (2.1)	38 (5.0)	
5	3 (4.7)	12 (1.6)		1 (2.1)	12 (1.6)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.279			0.168
1	14 (21.9)	173 (22.7)		10 (21.3)	172 (22.6)	
2	37 (57.8)	400 (52.4)		27 (57.4)	400 (52.6)	
3	9 (14.1)	171 (22.4)		8 (17.0)	169 (22.2)	
4	4 (6.2)	19 (2.5)		2 (4.3)	19 (2.5)	

EXERCISE_T7, n (%)			0.234			0.312
1	6 (9.4)	93 (12.2)		3 (6.4)	92 (12.1)	
2	11 (17.2)	90 (11.8)		9 (19.1)	90 (11.8)	
3	11 (17.2)	120 (15.7)		7 (14.9)	120 (15.8)	
4	18 (28.1)	275 (36.0)		14 (29.8)	275 (36.2)	
5	18 (28.1)	185 (24.2)		14 (29.8)	183 (24.1)	
Dataset 8						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		47	762	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	65.79 (10.75)	69.86 (9.77)	0.396
SEX_T7, n (%)			0.013			0.030
1	43 (67.2)	508 (66.6)		32 (68.1)	508 (66.7)	
BMI, mean (SD)	28.99 (5.07)	29.00 (4.54)	0.001	28.67 (4.79)	29.00 (4.54)	0.069
HEART_FAILURE_T7, n (%)			0.379			0.334
0	54 (84.4)	565 (74.0)		38 (80.9)	564 (74.0)	
1	1 (1.6)	76 (10.0)		1 (2.1)	76 (10.0)	
2	9 (14.1)	122 (16.0)		8 (17.0)	122 (16.0)	
ATRIAL_FIBRILLATION_T7, n (%)			0.215			0.165
0	40 (62.5)	545 (71.4)		30 (63.8)	545 (71.5)	
1	12 (18.8)	128 (16.8)		10 (21.3)	128 (16.8)	
2	12 (18.8)	90 (11.8)		7 (14.9)	89 (11.7)	
STROKE_T7, n (%)			0.128			0.059
2	8 (12.5)	130 (17.0)		7 (14.9)	130 (17.1)	
KIDNEY_DISEASE_T7, n (%)			0.209			0.112
0	53 (82.8)	653 (85.6)		39 (83.0)	652 (85.6)	
1	4 (6.2)	67 (8.8)		4 (8.5)	67 (8.8)	
2	7 (10.9)	43 (5.6)		4 (8.5)	43 (5.6)	
CANCER_T7, n (%)			0.202			0.199
0	56 (87.5)	620 (81.3)		40 (85.1)	619 (81.2)	
1	4 (6.2)	52 (6.8)		4 (8.5)	52 (6.8)	
2	4 (6.2)	91 (11.9)		3 (6.4)	91 (11.9)	
DIABETES_impu_new, n (%)			0.089			0.041
0	46 (71.9)	576 (75.5)		35 (74.5)	575 (75.5)	
1	15 (23.4)	151 (19.8)		10 (21.3)	151 (19.8)	
2	3 (4.7)	36 (4.7)		2 (4.3)	36 (4.7)	
Cons_GP_Times_impu, mean (SD)	4.22 (4.68)	5.06 (6.40)	0.149	4.79 (5.26)	5.05 (6.40)	0.045
Cons_Emergency_Times_impu, mean (SD)	0.28 (0.55)	0.34 (0.80)	0.085	0.23 (0.48)	0.34 (0.80)	0.161
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.61)	0.45 (0.98)	0.017	0.47 (1.79)	0.45 (0.98)	0.015
Cons_Specialist_Times_impu, mean (SD)	0.66 (1.73)	0.58 (3.05)	0.031	0.72 (1.95)	0.58 (3.05)	0.056
Cons_Clinic_Times_impu, mean (SD)	0.95 (2.18)	1.32 (4.56)	0.103	1.21 (2.48)	1.32 (4.57)	0.029
Alcohol_frequency_impu, n (%)			0.160			0.254
1	7 (10.9)	79 (10.4)		3 (6.4)	79 (10.4)	
2	14 (21.9)	160 (21.0)		11 (23.4)	159 (20.9)	
3	26 (40.6)	285 (37.4)		20 (42.6)	285 (37.4)	

4	10 (15.6)	166 (21.8)		7 (14.9)	166 (21.8)	
5	7 (10.9)	73 (9.6)		6 (12.8)	73 (9.6)	
Alcohol_units_impu, n (%)			0.205			0.234
0	8 (12.5)	81 (10.6)		4 (8.5)	81 (10.6)	
1	28 (43.8)	371 (48.6)		21 (44.7)	371 (48.7)	
2	24 (37.5)	233 (30.5)		19 (40.4)	232 (30.4)	
3	4 (6.2)	78 (10.2)		3 (6.4)	78 (10.2)	
Alcohol_units_6_impu, n (%)			0.300			0.314
1	34 (53.1)	448 (58.7)		23 (48.9)	448 (58.8)	
2	27 (42.2)	237 (31.1)		21 (44.7)	236 (31.0)	
3	2 (3.1)	55 (7.2)		2 (4.3)	55 (7.2)	
4	1 (1.6)	18 (2.4)		1 (2.1)	18 (2.4)	
5	0 (0.0)	5 (0.7)		0 (0.0)	5 (0.7)	
Smoke_impu, n (%)			0.230			0.228
1	4 (6.2)	86 (11.3)		4 (8.5)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		28 (59.6)	465 (61.0)	
4	22 (34.4)	200 (26.2)		15 (31.9)	199 (26.1)	
Snuff_chewing_tobacco_impu, n (%)			0.095			0.052
1	5 (7.8)	44 (5.8)		3 (6.4)	44 (5.8)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	40 (5.2)		2 (4.3)	40 (5.2)	
4	55 (85.9)	679 (89.0)		42 (89.4)	678 (89.0)	
Cod_liver_oil_omega3_impu, n (%)			0.205			0.189
0	41 (64.1)	558 (73.1)		32 (68.1)	557 (73.1)	
1	11 (17.2)	99 (13.0)		9 (19.1)	99 (13.0)	
2	4 (6.2)	28 (3.7)		1 (2.1)	28 (3.7)	
3	8 (12.5)	78 (10.2)		5 (10.6)	78 (10.2)	
FRUIT_UNITS_T7, mean (SD)	1.73 (1.41)	2.07 (1.96)	0.200	1.81 (1.54)	2.08 (1.96)	0.152
RED_MEAT_T7, n (%)			0.461			0.346
1	9 (14.1)	45 (5.9)		5 (10.6)	45 (5.9)	
2	15 (23.4)	162 (21.2)		13 (27.7)	162 (21.3)	
3	32 (50.0)	508 (66.6)		25 (53.2)	508 (66.7)	
4	8 (12.5)	39 (5.1)		4 (8.5)	38 (5.0)	
5	0 (0.0)	9 (1.2)		0 (0.0)	9 (1.2)	
FRUITS_VEG_BERRY_T7, n (%)			0.197			0.199
1	0 (0.0)	7 (0.9)		0 (0.0)	7 (0.9)	
2	4 (6.2)	31 (4.1)		3 (6.4)	31 (4.1)	
3	13 (20.3)	151 (19.8)		11 (23.4)	151 (19.8)	
4	15 (23.4)	215 (28.2)		13 (27.7)	214 (28.1)	
5	32 (50.0)	359 (47.1)		20 (42.6)	359 (47.1)	
LEAN_FISH_T7, n (%)			0.378			0.193
1	7 (10.9)	20 (2.6)		3 (6.4)	20 (2.6)	
2	8 (12.5)	102 (13.4)		6 (12.8)	101 (13.3)	
3	42 (65.6)	533 (69.9)		32 (68.1)	533 (69.9)	
4	5 (7.8)	96 (12.6)		5 (10.6)	96 (12.6)	
5	2 (3.1)	12 (1.6)		1 (2.1)	12 (1.6)	
FAT_FISH_T7, n (%)			0.335			0.353
1	9 (14.1)	88 (11.5)		8 (17.0)	87 (11.4)	
2	26 (40.6)	260 (34.1)		19 (40.4)	260 (34.1)	
3	25 (39.1)	367 (48.1)		17 (36.2)	367 (48.2)	

4	1 (1.6)	38 (5.0)		1 (2.1)	38 (5.0)	
5	3 (4.7)	10 (1.3)		2 (4.3)	10 (1.3)	
PHYS_ACTIVITY_LEISURE_T7, n (%)			0.326			0.203
1	14 (21.9)	174 (22.8)		9 (19.1)	174 (22.8)	
2	37 (57.8)	402 (52.7)		29 (61.7)	402 (52.8)	
3	9 (14.1)	175 (22.9)		8 (17.0)	175 (23.0)	
4	4 (6.2)	12 (1.6)		1 (2.1)	11 (1.4)	
EXERCISE_T7, n (%)			0.260			0.427
1	5 (7.8)	93 (12.2)		2 (4.3)	93 (12.2)	
2	10 (15.6)	89 (11.7)		10 (21.3)	89 (11.7)	
3	13 (20.3)	119 (15.6)		5 (10.6)	119 (15.6)	
4	18 (28.1)	274 (35.9)		15 (31.9)	273 (35.8)	
5	18 (28.1)	188 (24.6)		15 (31.9)	188 (24.7)	
Dataset 9						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		46	763	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	65.72 (10.23)	69.82 (9.82)	0.409
SEX_T7, n (%)			0.013			0.064
1	43 (67.2)	508 (66.6)		32 (69.6)	508 (66.6)	
BMI, mean (SD)	28.99 (5.07)	29.00 (4.54)	0.002	28.63 (4.49)	29.00 (4.54)	0.082
HEART_FAILURE_T7, n (%)			0.328			0.329
0	55 (85.9)	566 (74.2)		40 (87.0)	566 (74.2)	
1	2 (3.1)	74 (9.7)		2 (4.3)	74 (9.7)	
2	7 (10.9)	123 (16.1)		4 (8.7)	123 (16.1)	
ATRIAL_FIBRILLATION_T7, n (%)			0.215			0.127
0	40 (62.5)	543 (71.2)		31 (67.4)	543 (71.2)	
1	11 (17.2)	122 (16.0)		7 (15.2)	122 (16.0)	
2	13 (20.3)	98 (12.8)		8 (17.4)	98 (12.8)	
STROKE_T7, n (%)			0.096			0.126
2	9 (14.1)	134 (17.6)		6 (13.0)	134 (17.6)	
KIDNEY_DISEASE_T7, n (%)			0.226			0.102
0	53 (82.8)	655 (85.8)		40 (87.0)	655 (85.8)	
1	4 (6.2)	68 (8.9)		3 (6.5)	68 (8.9)	
2	7 (10.9)	40 (5.2)		3 (6.5)	40 (5.2)	
CANCER_T7, n (%)			0.198			0.164
0	56 (87.5)	618 (81.0)		40 (87.0)	618 (81.0)	
1	2 (3.1)	51 (6.7)		2 (4.3)	51 (6.7)	
2	6 (9.4)	94 (12.3)		4 (8.7)	94 (12.3)	
DIABETES_impu_new, n (%)			0.043			0.126
0	48 (75.0)	574 (75.2)		37 (80.4)	574 (75.2)	
1	13 (20.3)	147 (19.3)		7 (15.2)	147 (19.3)	
2	3 (4.7)	42 (5.5)		2 (4.3)	42 (5.5)	
Cons_GP_Times_impu, mean (SD)	3.28 (2.58)	4.86 (5.76)	0.353	3.37 (2.78)	4.86 (5.76)	0.329
Cons_Emergency_Times_impu, mean (SD)	0.25 (0.53)	0.34 (0.77)	0.129	0.20 (0.45)	0.34 (0.77)	0.221
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.61)	0.45 (0.99)	0.012	0.43 (1.80)	0.45 (0.99)	0.012

Cons_Specialist_Times_impu, mean (SD)	0.47 (0.96)	0.56 (3.06)	0.039	0.52 (1.03)	0.56 (3.06)	0.016
Cons_Clinic_Times_impu, mean (SD)	"0.77 (1.46)	1.19 (3.56)	0.158	0.91 (1.63)	1.19 (3.56)	0.102
Alcohol_frequency_impu, n (%)			0.160			0.152
1	7 (10.9)	79 (10.4)		4 (8.7)	79 (10.4)	
2	14 (21.9)	160 (21.0)		8 (17.4)	160 (21.0)	
3	26 (40.6)	285 (37.4)		20 (43.5)	285 (37.4)	
4	10 (15.6)	166 (21.8)		9 (19.6)	166 (21.8)	
5	7 (10.9)	73 (9.6)		5 (10.9)	73 (9.6)	
Alcohol_units_impu, n (%)			0.201			0.187
0	8 (12.5)	81 (10.6)		5 (10.9)	81 (10.6)	
1	28 (43.8)	371 (48.6)		19 (41.3)	371 (48.6)	
2	24 (37.5)	234 (30.7)		18 (39.1)	234 (30.7)	
3	4 (6.2)	77 (10.1)		4 (8.7)	77 (10.1)	
Alcohol_units_6_impu, n (%)			0.300			0.222
1	34 (53.1)	449 (58.8)		25 (54.3)	449 (58.8)	
2	27 (42.2)	236 (30.9)		18 (39.1)	236 (30.9)	
3	2 (3.1)	56 (7.3)		2 (4.3)	56 (7.3)	
4	1 (1.6)	18 (2.4)		1 (2.2)	18 (2.4)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.290
1	4 (6.2)	86 (11.3)		4 (8.7)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		25 (54.3)	465 (60.9)	
4	22 (34.4)	200 (26.2)		17 (37.0)	200 (26.2)	
Snuff_chewing_tobacco_impu, n (%)			0.093			0.043
1	5 (7.8)	45 (5.9)		3 (6.5)	45 (5.9)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		2 (4.3)	39 (5.1)	
4	55 (85.9)	679 (89.0)		41 (89.1)	679 (89.0)	
Cod_liver_oil_omega3_impu, n (%)			0.203			0.137
0	41 (64.1)	559 (73.3)		31 (67.4)	559 (73.3)	
1	11 (17.2)	101 (13.2)		7 (15.2)	101 (13.2)	
2	4 (6.2)	30 (3.9)		2 (4.3)	30 (3.9)	
3	8 (12.5)	73 (9.6)		6 (13.0)	73 (9.6)	
FRUIT_UNITS_T7, mean (SD)	1.84 (1.48)	2.10 (1.96)	0.145	1.91 (1.50)	2.10 (1.96)	0.104
RED_MEAT_T7, n (%)			0.427			0.358
1	9 (14.1)	46 (6.0)		6 (13.0)	46 (6.0)	
2	15 (23.4)	161 (21.1)		12 (26.1)	161 (21.1)	
3	33 (51.6)	506 (66.3)		27 (58.7)	506 (66.3)	
4	7 (10.9)	39 (5.1)		1 (2.2)	39 (5.1)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FRUITS_VEG_BERRY_T7, n (%)			0.204			0.233
1	0 (0.0)	8 (1.0)		0 (0.0)	8 (1.0)	
2	4 (6.2)	30 (3.9)		2 (4.3)	30 (3.9)	
3	13 (20.3)	152 (19.9)		12 (26.1)	152 (19.9)	
4	15 (23.4)	213 (27.9)		10 (21.7)	213 (27.9)	
5	32 (50.0)	360 (47.2)		22 (47.8)	360 (47.2)	
LEAN_FISH_T7, n (%)			0.444			0.224
1	8 (12.5)	19 (2.5)		1 (2.2)	19 (2.5)	

2	8 (12.5)	102 (13.4)		6 (13.0)	102 (13.4)	
3	43 (67.2)	534 (70.0)		35 (76.1)	534 (70.0)	
4	5 (7.8)	97 (12.7)		4 (8.7)	97 (12.7)	
5	0 (0.0)	11 (1.4)		0 (0.0)	11 (1.4)	
FAT_FISH_T7, n (%)			0.299			0.267
1	8 (12.5)	86 (11.3)		6 (13.0)	86 (11.3)	
2	29 (45.3)	261 (34.2)		20 (43.5)	261 (34.2)	
3	25 (39.1)	368 (48.2)		18 (39.1)	368 (48.2)	
4	1 (1.6)	38 (5.0)		1 (2.2)	38 (5.0)	
5	1 (1.6)	10 (1.3)		1 (2.2)	10 (1.3)	
PHYS_ACTIVITY_LEISURE_ T7, n (%)			0.306			0.161
1	14 (21.9)	178 (23.3)		10 (21.7)	178 (23.3)	
2	37 (57.8)	401 (52.6)		25 (54.3)	401 (52.6)	
3	9 (14.1)	170 (22.3)		9 (19.6)	170 (22.3)	
4	4 (6.2)	14 (1.8)		2 (4.3)	14 (1.8)	
EXERCISE_T7, n (%)			0.258			0.390
1	5 (7.8)	93 (12.2)		2 (4.3)	93 (12.2)	
2	10 (15.6)	91 (11.9)		9 (19.6)	91 (11.9)	
3	12 (18.8)	119 (15.6)		8 (17.4)	119 (15.6)	
4	18 (28.1)	275 (36.0)		13 (28.3)	275 (36.0)	
5	19 (29.7)	185 (24.2)		14 (30.4)	185 (24.2)	
Dataset 10						
	Before matching			**After matching**		
	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD	Not anti-hypertensive drug user	Anti-hypertensive drug user	SMD
n	64	763		46	760	
AGE, mean (SD)	61.95 (11.84)	69.82 (9.82)	0.723	64.76 (11.33)	69.87 (9.80)	0.482
SEX_T7, n (%)			0.013			0.017
1	43 (67.2)	508 (66.6)		31 (67.4)	506 (66.6)	
BMI, mean (SD)	28.99 (5.07)	29.00 (4.54)	0.001	28.49 (4.64)	29.00 (4.54)	0.110
HEART_FAILURE_T7, n (%)			0.385			0.327
0	55 (85.9)	565 (74.0)		38 (82.6)	562 (73.9)	
1	1 (1.6)	73 (9.6)		1 (2.2)	73 (9.6)	
2	8 (12.5)	125 (16.4)		7 (15.2)	125 (16.4)	
ATRIAL_FIBRILLATION_T7, n (%)			0.197			0.206
0	40 (62.5)	543 (71.2)		29 (63.0)	542 (71.3)	
1	12 (18.8)	123 (16.1)		8 (17.4)	123 (16.2)	
2	12 (18.8)	97 (12.7)		9 (19.6)	95 (12.5)	
STROKE_T7, n (%)			0.135			0.055
2	8 (12.5)	132 (17.3)		7 (15.2)	131 (17.2)	
KIDNEY_DISEASE_T7, n (%)			0.144			0.085
0	53 (82.8)	653 (85.6)		39 (84.8)	651 (85.7)	
1	5 (7.8)	67 (8.8)		5 (10.9)	67 (8.8)	
2	6 (9.4)	43 (5.6)		2 (4.3)	42 (5.5)	
CANCER_T7, n (%)			0.176			0.114
0	56 (87.5)	619 (81.1)		39 (84.8)	616 (81.1)	
1	3 (4.7)	52 (6.8)		3 (6.5)	52 (6.8)	
2	5 (7.8)	92 (12.1)		4 (8.7)	92 (12.1)	
DIABETES_impu_new, n (%)			0.093			0.117
0	46 (71.9)	574 (75.2)		35 (76.1)	572 (75.3)	

1	14 (21.9)	155 (20.3)		8 (17.4)	155 (20.4)	
2	4 (6.2)	34 (4.5)		3 (6.5)	33 (4.3)	
Cons_GP_Times_impu, mean (SD)	3.89 (4.49)	4.80 (5.31)	0.185	4.22 (5.03)	4.79 (5.32)	0.111
Cons_Emergency_Times_impu, mean (SD)	0.27 (0.54)	0.33 (0.76)	0.092	0.26 (0.53)	0.33 (0.76)	0.101
Cons_Hospital_Times_impu, mean (SD)	0.47 (1.61)	0.45 (0.98)	0.013	0.54 (1.85)	0.45 (0.99)	0.062
Cons_Specialist_Times_impu, mean (SD)	0.80 (2.74)	0.56 (3.11)	0.082	0.98 (3.19)	0.53 (3.03)	0.145
Cons_Clinic_Times_impu, mean (SD)	0.66 (1.22)	1.15 (3.47)	0.188	0.78 (1.38)	1.15 (3.47)	0.138
Alcohol_frequency_impu, n (%)			0.171			0.270
1	6 (9.4)	79 (10.4)		2 (4.3)	79 (10.4)	
2	14 (21.9)	160 (21.0)		9 (19.6)	159 (20.9)	
3	27 (42.2)	285 (37.4)		21 (45.7)	283 (37.2)	
4	10 (15.6)	166 (21.8)		9 (19.6)	166 (21.8)	
5	7 (10.9)	73 (9.6)		5 (10.9)	73 (9.6)	
Alcohol_units_impu, n (%)			0.162			0.305
0	7 (10.9)	81 (10.6)		2 (4.3)	81 (10.7)	
1	28 (43.8)	371 (48.6)		21 (45.7)	370 (48.7)	
2	24 (37.5)	233 (30.5)		19 (41.3)	231 (30.4)	
3	5 (7.8)	78 (10.2)		4 (8.7)	78 (10.3)	
Alcohol_units_6_impu, n (%)			0.325			0.319
1	33 (51.6)	449 (58.8)		26 (56.5)	448 (58.9)	
2	28 (43.8)	235 (30.8)		18 (39.1)	233 (30.7)	
3	2 (3.1)	55 (7.2)		2 (4.3)	55 (7.2)	
4	1 (1.6)	20 (2.6)		0 (0.0)	20 (2.6)	
5	0 (0.0)	4 (0.5)		0 (0.0)	4 (0.5)	
Smoke_impu, n (%)			0.230			0.292
1	4 (6.2)	86 (11.3)		3 (6.5)	86 (11.3)	
2	1 (1.6)	12 (1.6)		0 (0.0)	12 (1.6)	
3	37 (57.8)	465 (60.9)		27 (58.7)	464 (61.1)	
4	22 (34.4)	200 (26.2)		16 (34.8)	198 (26.1)	
Snuff_chewing_tobacco_impu, n (%)			0.093			0.090
1	5 (7.8)	45 (5.9)		2 (4.3)	45 (5.9)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
3	4 (6.2)	39 (5.1)		3 (6.5)	39 (5.1)	
4	55 (85.9)	679 (89.0)		41 (89.1)	676 (88.9)	
Cod_liver_oil_omega3_impu, n (%)			0.179			0.262
0	42 (65.6)	559 (73.3)		30 (65.2)	557 (73.3)	
1	12 (18.8)	99 (13.0)		10 (21.7)	98 (12.9)	
2	3 (4.7)	31 (4.1)		1 (2.2)	31 (4.1)	
3	7 (10.9)	74 (9.7)		5 (10.9)	74 (9.7)	
FRUIT_UNITS_T7, mean (SD)	1.77 (1.38)	2.06 (1.97)	0.174	1.93 (1.50)	2.05 (1.96)	0.068
RED_MEAT_T7, n (%)			0.440			0.281
1	10 (15.6)	46 (6.0)		6 (13.0)	46 (6.1)	
2	14 (21.9)	160 (21.0)		11 (23.9)	159 (20.9)	
3	32 (50.0)	511 (67.0)		26 (56.5)	510 (67.1)	
4	7 (10.9)	36 (4.7)		2 (4.3)	35 (4.6)	
5	1 (1.6)	10 (1.3)		1 (2.2)	10 (1.3)	

FRUITS_VEG_BERRY_T7, n (%)			0.257			0.241
1	0 (0.0)	9 (1.2)		0 (0.0)	9 (1.2)	
2	5 (7.8)	30 (3.9)		3 (6.5)	30 (3.9)	
3	11 (17.2)	153 (20.1)		9 (19.6)	152 (20.0)	
4	15 (23.4)	212 (27.8)		10 (21.7)	212 (27.9)	
5	33 (51.6)	359 (47.1)		24 (52.2)	357 (47.0)	
LEAN_FISH_T7, n (%)			0.452			0.275
1	8 (12.5)	19 (2.5)		3 (6.5)	18 (2.4)	
2	9 (14.1)	100 (13.1)		6 (13.0)	99 (13.0)	
3	42 (65.6)	533 (69.9)		32 (69.6)	532 (70.0)	
4	5 (7.8)	99 (13.0)		5 (10.9)	99 (13.0)	
5	0 (0.0)	12 (1.6)		0 (0.0)	12 (1.6)	
FAT_FISH_T7, n (%)			0.284			0.254
1	8 (12.5)	88 (11.5)		6 (13.0)	87 (11.4)	
2	29 (45.3)	263 (34.5)		19 (41.3)	261 (34.3)	
3	25 (39.1)	367 (48.1)		20 (43.5)	367 (48.3)	
4	1 (1.6)	35 (4.6)		1 (2.2)	35 (4.6)	
5	1 (1.6)	10 (1.3)		0 (0.0)	10 (1.3)	
PHYS_ACTIVITY_LEISURE_ T7, n (%)			0.280			0.141
1	14 (21.9)	166 (21.8)		10 (21.7)	165 (21.7)	
2	37 (57.8)	405 (53.1)		27 (58.7)	404 (53.2)	
3	9 (14.1)	173 (22.7)		8 (17.4)	172 (22.6)	
4	4 (6.2)	19 (2.5)		1 (2.2)	19 (2.5)	
EXERCISE_T7, n (%)			0.222			0.263
1	6 (9.4)	93 (12.2)		3 (6.5)	93 (12.2)	
2	10 (15.6)	88 (11.5)		8 (17.4)	87 (11.4)	
3	12 (18.8)	120 (15.7)		7 (15.2)	120 (15.8)	
4	18 (28.1)	274 (35.9)		15 (32.6)	273 (35.9)	
5	18 (28.1)	188 (24.6)		13 (28.3)	187 (24.6)	

SMD, standardized mean difference

Supplementary table 7: Pooled results from the sensitivity analysis for the logistic regression analyses of the multiple imputed datasets, using propensity score matching without replacement.*

Exposure variable	Outcome variable	Odds ratio	95 % confidence interval
Use of lipid lowering drugs	Achievement of treatment goal for LDL-cholesterol	17.3	5.3-56.4
Use of antihypertensive drugs	Achievement of treatment goal for blood pressure	1.5	0.6-3.6

* Number of cases varied between datasets and can be found in supplementary tables 5 and 6

Paper II

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ORIGINAL ARTICLE

Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data

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Abstract

Objective: To validate self-reported use of medications for secondary prevention of coronary heart disease (CHD) in a population-based health study by comparing self-report with pharmacy dispensing data, and explore different methods for defining medication use in prescription databases.

Study design and setting: Self-reported medication use among participants with CHD ($n = 1483$) from the seventh wave of the Tromsø Study was linked with the Norwegian Prescription Database (NorPD). Cohen's kappa, sensitivity, specificity, and positive and negative predictive values were calculated, using NorPD as the reference standard. Medication use in NorPD was defined in three ways; fixed-time window of 180 days, and legend-time method assuming a daily dose of one dosage unit or one defined daily dose (DDD).

Results: Kappa-values for antihypertensive drugs, lipid-lowering drugs and acetylsalicylic acid all showed substantial agreement (kappa $\geq$0.61). Validity varied depending on the method used for defining medication use in NorPD. Applying a fixed-time window gave higher agreement, positive predictive values and specificity compared with the legend-time methods.

Conclusion: Self-reported use of medication for secondary prevention of CHD shows high validity when compared with pharmacy dispensing data. For CHD medications, fixed-time window appears to be the most appropriate method for defining medication use in prescription databases.

Keywords: Medication use; validation; agreement; population-based study; prescription database

What is new?

Key findings

- Self-reported use of lipid-lowering drugs, antihypertensive drugs and acetylsalicylic acid among patients with coronary heart disease showed high agreement when compared with pharmacy dispensing data. Using a fixed-time window to define current medication use gave higher agreement, positive predictive values and specificity compared with the legend-time methods.

What this adds to what is known?

- Self-reported medication use for coronary heart disease collected with a questionnaire combining pre-specified and open-ended questions gives a valid measure of medication use.
- For coronary heart disease medication, a fixed-time window is better than legend-time methods in defining current use from prescription data. If legend-time is used and the prescribed dose is unavailable, assuming a daily dose of one dosage unit is a better choice than one defined daily dose for these medications.

Abbreviations: ASA, acetylsalicylic acid; CHD, coronary heart disease; DDD, defined daily dose; LLD, lipid-lowering drug; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value.

Declarations of competing interest: None.

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What is the implication, what should change now?

- Though a combination of self-report and prescription data classifies medication exposure most accurately, self-reported information on medication for secondary prevention of coronary heart disease has adequate validity to be used for epidemiological research if prescription data is unavailable.
- When investigating current use of medications for coronary heart disease using prescription databases, fixed-time window appears to be a more appropriate method than the legend-time method.

1. Introduction

Medication use is an important factor in many epidemiological studies, either as exposure or outcome. Poor measurement of medication use can lead to over- or underestimation of true associations and risks [1].

There are several ways to measure medication use, where self-reported use, e.g. questionnaires or interviews, and pharmacy dispensing data are common methods. Unfortunately, no method provides information about the true medication exposure. Self-reported use may be biased by poor recall and underreporting of socially stigmatized medication classes [2,3]. Despite being collected objectively and nondifferentially, dispensing data cannot account for secondary nonadherence, i.e., dispensed medication is not necessarily used. It may also be prone to selection bias as some data sources include only reimbursed medications, and others are based on claims from selected insurance companies or pharmacies [4–10]. A few countries, like the Scandinavian countries, have complete prescription registries that include all prescription-based medications dispensed from pharmacies [11].

Several studies have compared medication use measurements from different data sources [4–10,12–17]. Most studies find good agreement and validity between self-reported and dispensing data when investigating medications used for long-term conditions. Results are less consistent for medications used as needed [9,10,12,13]. Cardiovascular medications, such as antihypertensive drugs, lipid-lowering drugs (LLDs) and antiplatelet drugs, are normally used on a daily basis, and agreement and validity between different data sources are usually found to be high [4–7,9,10,12–17]. However, few studies have investigated this in a population with established coronary heart disease (CHD) or compared data from complete prescription registries with self-reported data from a large population study.

A methodological concern with prescription registry data entails defining "current medication use". The two most commonly applied methods are fixed-time window and legend-time duration. Fixed-time window is most frequently applied and defines participants as medication-users if they have been dispensed the medication within a set time window before an index date [8,17]. The legend-time method uses information from the last prescription dispensed before the index date to calculate whether the dispensed medication will last to the index date [8,17]. Some studies have compared the two methods, but no consensus have been reached concerning which is the most appropriate for defining current medication use [8,12,18].

This study aimed to validate self-reported use of medications for secondary prevention of CHD in a population-based health study by comparing self-report with pharmacy dispensing data using the Norwegian Prescription Database (NorPD) as the reference standard, and exploring different methods for defining medication use in NorPD.

2. Methods

2.1. The Tromsø study

The Tromsø Study is a population-based health study that has been conducted seven times from 1974 to 2016 [19]. The study includes inhabitants in the municipality of Tromsø, Norway, a town with approximately 73,000 inhabitants in 2016. The present study used data collected during 2015-16 from the seventh wave of the Tromsø Study (Tromsø 7), where all inhabitants $\geq$ 40 years (n = 32,591) were invited to participate. The response rate was 65% (n = 21,083).

Participation in Tromsø 7 included answering two questionnaires, donating blood samples and going through clinical examinations. Most questions about diseases and medication use were posed in questionnaire 1, which could be answered either on paper or electronically anytime between invitation and attending the health examination. Links to the questionnaires can be found at the Tromsø Study's webpage [19].

2.2. The Norwegian Prescription Database (NorPD)

NorPD contains complete information about all prescribed medications dispensed from Norwegian pharmacies to individuals since January 2004. Medications used in hospitals/nursing homes and over-the-counter medications are not included. We included the following variables from NorPD: date of dispensing and information on medications dispensed (including Anatomical Therapeutic Chemical (ATC) code, and number of dosage units and defined daily doses (DDDs) dispensed [20]). DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [20].

2.3. Study population

From Tromsø 7, we included participants reporting established CHD (n = 1483). CHD was defined as reporting either previous myocardial infarction, present or previous

angina pectoris, previous percutaneous coronary intervention or coronary artery bypass graft surgery.

2.4. Medications included

We included medications for secondary prevention of CHD (Fig. 1), which according to the prevailing European guidelines in 2015/2016 was acetylsalicylic acid (ASA), LLDs (mainly statins) and antihypertensive drugs (angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium-channel blockers (CCBs), thiazides and other antihypertensives) [21].

2.5. Defining medication use

In Tromsø 7, medication use was self-reported through i) questions about specific medication use and ii) participants listing the brand names for all medications used regularly the previous four weeks. We defined users of LLDs and antihypertensive drugs as participants answering "currently" to the two specific questions "*Do you use, or have you used cholesterol-lowering drugs?*" and *"Do you use, or have you used blood pressure lowering drugs?",* (response alternatives were "currently", "previously, not now" and "never used") and/or listing the brand name of an LLD or antihypertensive drug, respectively. We defined users of ASA as participants answering "yes" when asked *"If you have used analgesics and anti-inflammatory medication regularly in the past year - did you use "Baby" or low dose acetylsalicylic acid (ASA), i.e. Acetylsalisylsyre®, Albyl-E®, Asasantin Retard® (75/160 mg per tablet)?"* (response alternatives were "yes" and "no"), or denoting a brand name for ASA.

From NorPD, current use was defined by three approaches; one using a fixed-time window and two using the legend-time method (Fig. 2). For all approaches, index date was the day the participants completed the Tromsø 7 questionnaire. Using a fixed-time window definition, medication-users were participants who had been dispensed at least one prescription within 180 days before index date. A sensitivity analysis was performed using time windows of 90 and 365 days. The legend-time method requires knowledge about the duration of use. As prescribed daily dose is not available in NorPD, we calculated the duration supplied assuming the daily dose was equal to: i) one dosage unit (e.g. tablet, capsule etc.), and ii) one DDD. In both legend-time approaches, we added 10% to the duration to account for imperfect adherence before assessing whether the duration of the last dispensation covered the index date. Sensitivity analyses were performed by not adding any additional units/DDDs, and by adding 20% additional units/DDDs.

2.6. Statistical analysis

Data from Tromsø 7 was linked with NorPD data using the unique national identity number assigned to all citizens in Norway. NorPD performed the record linkage according to standard procedures. Agreement between Tromsø 7 and NorPD was measured by percent observed agreement and Cohen's kappa. Kappa-values were interpreted as proposed by Landis and Koch: poor (<0.00), slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00) [22].

To determine the validity of self-reported medication use, we calculated sensitivity and specificity using NorPD as the reference standard. Positive (PPV) and negative (NPV) predictive values were also calculated.

Analyses were conducted applying IBM SPSS 25 for Windows. Confidence intervals were calculated using VassarStats [23,24]. Results are expressed as proportions and kappa-values with 95% confidence intervals.

2.7. Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics of North Norway (2015/1775) and had an approved Data Protection Impact Assessment from UiT The Arctic University of Norway. All participants in the Tromsø Study have given written informed consent for their data to be used in research.

3. Results

In the study population (n = 1483), 70% were male and mean age was 68.7 (standard deviation 10.8) years. Medication use is shown in Table 1.

Agreement was substantial for antihypertensive drugs, LLDs and ASA, with kappa-values ≥0.61 (Table 2). An exception was for ASA when using either of the legend-time methods, in which case the kappa-value was 0.60. The fixed-time window method gave higher agreement than either of the legend-time methods, both in terms of percent agreement and kappa. For antihypertensive drugs, the kappa-value showed an almost perfect agreement when using a fixed-time window.

Among participants where the two data sources did not agree, more participants were identified as ASA-users in NorPD than in Tromsø 7, while the result was opposite for LLD-users (Table 2). For antihypertensive drugs, more participants were identified as users in NorPD than in Tromsø 7 when using a fixed-time window, but opposite when using the legend-time methods.

PPV was high for all three main medication classes, which shows that when participants report using these medications, the likelihood that they had it dispensed is high. Highest values were found using fixed-time window, while legend-time with DDD gave the lowest values. NPV was high for antihypertensive drugs and LLDs but lower

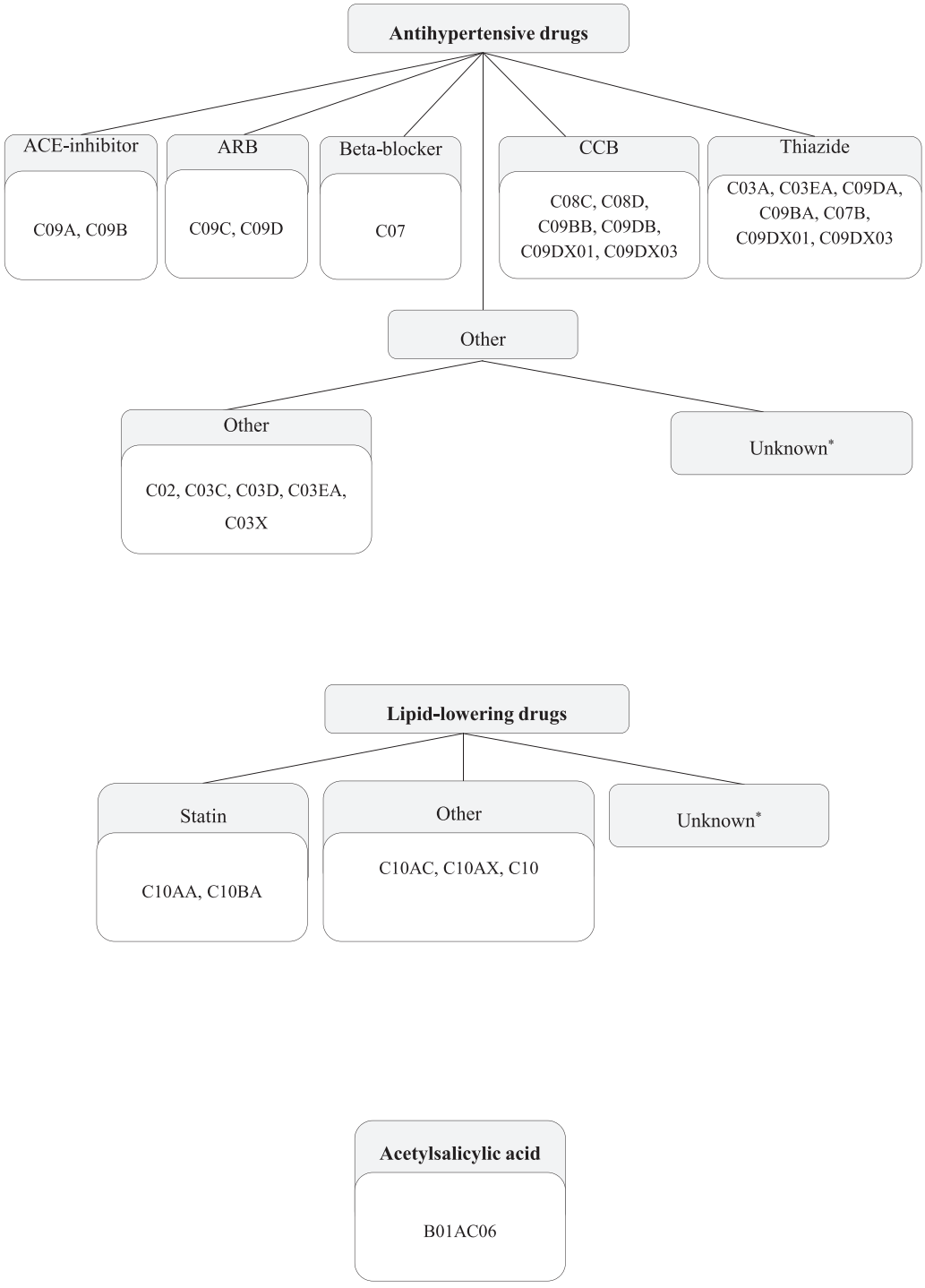

Fig. 1. Overview of included ATC-codes and aggregation into medication groups.
*When, instead of brand name, the participants in free text reported using medication interpretable as "blood pressure lowering" or "cholesterol lowering", it was registered under the respective medication category.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATC, anatomical therapeutic chemical classification system; CCB, calcium-channel blocker.

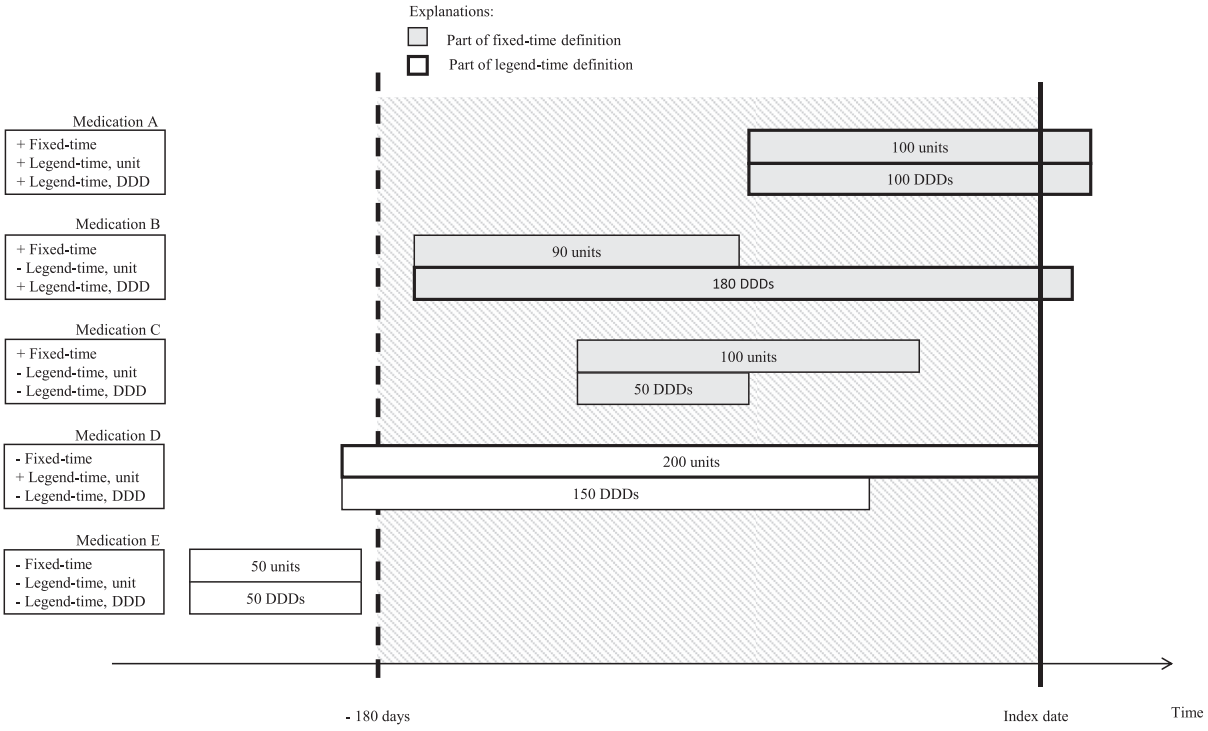

Fig. 2. The three different methods used to define medication users in NorPD. Index date is the day of questionnaire completion. Using fixed-time window, participants were defined as medication-users if they had a medication dispensed ≤180 days before index date. The legend-time methods defined a participant as user if the supply of medication most recently dispensed would last past the index date, assuming a daily dosage of either one unit (e.g., tablet) or one DDD. Medications A, B and C are in use according to fixed-time window; A and D are in use when applying legend-time with one unit a day; A and B are in use applying legend-time with one DDD a day. Medication E is not defined as in use by any of the methods. Abbreviations: DDD, defined daily dose; NorPD, Norwegian Prescription Database

Table 1. Prevalence of use (*n* (%)) of medications for secondary prevention of coronary heart disease in Tromsø 7 and the three approaches for defining medication use in NorPD ($n = 1483$)

	Tromsø 7		NorPD, Fixed-time		NorPD, Legend-time, Unit		NorPD, Legend-time, DDD	
Antihypertensive drugs	1069	(72.1)	1087	(73.3)	1032	(69.6)	865	(58.3)
Lipid-lowering drugs	1133	(76.4)	1074	(72.4)	960	(64.7)	928	(62.6)
Acetylsalicylic acid	980	(66.1)	1098	(74.0)	991	(66.8)	991	(66.8)

Abbreviations: DDD, defined daily dose; NorPD, Norwegian Prescription Database

for ASA. For NPV, the legend-time methods and especially using DDDs gave the highest values, but the difference between methods was small.

Sensitivity was also high for all three main medication classes. This indicates that a high proportion of those registered as users in NorPD also self-reported use of these medications in Tromsø 7. Specificity was lower than the sensitivity for antihypertensive drugs and LLDs, but higher for ASA. The specificity was lowest when using the legend-time methods, and especially with one DDD as the daily dosage.

Among the antihypertensive drugs, an almost perfect agreement was found for angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs) and calcium-channel blockers (CCBs) when using fixed-time window, while the legend-time methods gave substantial to almost perfect agreements (Table 3). The kappa-values for thiazides showed substantial agreement. For beta-blockers, agreement was substantial when using fixed-time window and legend-time method with one unit a day, and fair with legend-time method with one DDD a day. For statins, agreement was substantial when using the fixed-time window method and fair with either legend-time method.

Sensitivity analyses showed higher agreement for a 180 days than a 90 days fixed-time window, and the main analysis (with 10% extra added to the duration) for the legend-time methods showed higher agreement than no addition. Using a 365 days fixed-time window or adding 20% to the duration in the legend-time methods gave results similar to the main analysis (supplementary tables A.1-A.3).

Table 2. Self-reported use of antihypertensive drugs, lipid-lowering drugs and acetylsalicylic acid in the Tromsø 7 questionnaire compared with the three approaches for defining medication use in NorPD ($n = 1483$)

	Antihypertensive drugs			Lipid-lowering drugs			Acetylsalicylic acid		
	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed- time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD
Observed agreement*, *n*	1371	1346	1221	1358	1276	1242	1287	1216	1216
(%)	(92.5)	(90.8)	(82.3)	(91.6)	(86.0)	(82.0)	(86.8)	(82.0)	(82.0)
Kappa	0.81	0.78	0.62	0.78	0.67	0.63	0.69	0.60	0.60
(95% CI)	(0.78–0.84)	(0.74–0.81)	(0.58–0.66)	(0.74–0.82)	(0.63–0.71)	(0.55–0.64)	(0.65–0.73)	(0.55–0.64)	(0.55–0.64)
Both sources, *n*	1022	982	836	1041	943	910	941	852	852
(%)	(68.9)	(66.2)	(56.4)	(70.2)	(63.6)	(61.4)	(63.5)	(57.5)	(57.5)
Tromsø 7 only, *n*	47	87	233	92	190	223	39	128	128
(%)	(3.2)	(5.9)	(15.7)	(6.2)	(12.8)	(15.0)	(2.6)	(8.6)	(8.6)
NorPD only, *n*	65	50	29	33	17	18	157	139	139
(%)	(4.4)	(3.4)	(2.0)	(2.2)	(1.2)	(1.2)	(10.6)	(9.4)	(9.4)
Neither, *n*	349	364	385	317	333	332	346	364	364
(%)	(23.5)	(24.6)	(26.0)	(21.4)	(22.5)	(22.4)	(23.3)	(24.6)	(24.6)
Sensitivity	0.94	0.95	0.97	0.97	0.98	0.98	0.86	0.86	0.86
(95% CI)	(0.92–0.95)	(0.94–0.96)	(0.95–0.98)	(0.96–0.98)	(0.97–0.99)	(0.97–0.99)	(0.84–0.88)	(0.84–0.88)	(0.84–0.88)
Specificity	0.88	0.81	0.62	0.78	0.64	0.60	0.90	0.74	0.74
(95% CI)	(0.84–0.91)	(0.77–0.84)	(0.58–0.66)	(0.73–0.81)	(0.59–0.68)	(0.56–0.64)	(0.86–0.93)	(0.70–0.78)	(0.70–0.78)
PPV	0.96	0.92	0.78	0.92	0.83	0.80	0.96	0.87	0.87
(95% CI)	(0.94–0.97)	(0.90–0.93)	(0.76–0.81)	(0.90–0.93)	(0.81–0.85)	(0.78–0.83)	(0.95–0.97)	(0.85–0.89)	(0.85–0.89)
NPV	0.84	0.88	0.93	0.91	0.95	0.95	0.69	0.72	0.72
(95% CI)	(0.80–0.88)	(0.84–0.91)	(0.90–0.95)	(0.87–0.93)	(0.92–0.97)	(0.92–0.97)	(0.65–0.73)	(0.68–0.76)	(0.68–0.76)

* Includes agreement of both users and nonusers.

Abbreviations: CI, confidence interval; DDD, defined daily dose; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

Table 3. Self-reported use of statins and different classes of antihypertensive drugs in the Tromsø 7 questionnaire compared with the three approaches for defining medication use in NorPD ($n = 1483$)

	ACE-inhibitor			ARB			Beta-blocker			CCB			Thiazide			Statin		
	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD	Fixed-time	Legend-time, Unit	Legend-time, DDD
Observed agreement*, *n*	1426	1421	1410	1391	1376	1372	1308	1277	1058	1411	1401	1412	1395	1385	1384	1218	1178	1162
(%)	(96.2)	(95.9)	(95.1)	(93.8)	(92.8)	(92.5)	(88.2)	(86.1)	(71.3)	(95.2)	(94.5)	(95.2)	(94.1)	(93.4)	(93.3)	(82.1)	(79.4)	(78.4)
Kappa	0.85	0.83	0.80	0.83	0.80	0.79	0.77	0.72	0.40	0.83	0.80	0.83	0.76	0.71	0.71	0.61	0.57	0.55
(95% CI)	(0.82–0.89)	(0.79–0.87)	(0.75–0.84)	(0.80–0.87)	(0.76–0.84)	(0.76–0.83)	(0.73–0.80)	(0.69–0.76)	(0.36–0.44)	(0.80–0.87)	(0.76–0.84)	(0.79–0.87)	(0.71–0.80)	(0.66–0.77)	(0.66–0.76)	(0.57–0.65)	(0.52–0.61)	(0.50–0.59)
Both sources, *n*	199	184	174	319	294	292	643	595	309	226	208	215	164	148	147	839	761	742
(%)	(13.4)	(12.4)	(11.7)	(21.5)	(19.8)	(19.7)	(43.4)	(40.1)	(20.8)	(15.2)	(14.0)	(14.5)	(11.1)	(10.0)	(9.9)	(56.6)	(51.3)	(50.0)
Tromsø 7 only, *n*	6	21	31	7	32	34	27	75	361	5	23	16	7	23	24	51	129	148
(%)	(0.4)	(1.4)	(2.1)	(0.5)	(2.2)	(2.3)	(1.8)	(5.1)	(24.3)	(0.3)	(1.6)	(1.2)	(0.5)	(1.6)	(1.6)	(3.4)	(8.7)	(10.0)
NorPD only, *n*	51	41	42	85	75	77	148	131	64	67	59	55	81	75	75	214	176	173
(%)	(3.4)	(2.8)	(2.8)	(5.7)	(5.1)	(5.2)	(10.0)	(8.8)	(4.3)	(4.5)	(4.0)	(3.7)	(5.5)	(5.1)	(5.1)	(14.4)	(11.9)	(11.7)
Neither, *n*	1227	1237	1236	1072	1082	1080	665	682	749	1185	1193	1197	1231	1237	1237	379	417	420
(%)	(82.7)	(83.4)	(83.4)	(72.3)	(73.0)	(72.8)	(44.8)	(46.0)	(50.5)	(79.9)	(80.5)	(80.7)	(83.0)	(83.4)	(83.4)	(25.6)	(28.1)	(28.3)
Sensitivity	0.80	0.82	0.81	0.79	0.80	0.79	0.81	0.82	0.83	0.77	0.78	0.80	0.67	0.66	0.66	0.80	0.81	0.81
(95% CI)	(0.74–0.84)	(0.76–0.87)	(0.75–0.86)	(0.75–0.83)	(0.75–0.84)	(0.75–0.83)	(0.78–0.84)	(0.79–0.85)	(0.79–0.87)	(0.72–0.82)	(0.72–0.83)	(0.74–0.84)	(0.61–0.73)	(0.60–0.73)	(0.60–0.72)	(0.77–0.82)	(0.79–0.84)	(0.78–0.84)
Specificity	1.00	0.98	0.98	0.99	0.97	0.97	0.96	0.90	0.68	1.00	0.98	0.99	0.99	0.98	0.98	0.88	0.76	0.74
(95% CI)	(0.99–1.00)	(0.97–0.99)	(0.97–0.98)	(0.99–1.00)	(0.96–0.98)	(0.96–0.98)	(0.94–0.97)	(0.88–0.92)	(0.65–0.70)	(0.99–1.00)	(0.97–0.99)	(0.98–0.99)	(0.99–1.00)	(0.97–0.99)	(0.97–0.99)	(0.85–0.91)	(0.73–0.80)	(0.70–0.78)
PPV	0.97	0.90	0.85	0.98	0.90	0.90	0.96	0.89	0.46	0.98	0.90	0.93	0.96	0.87	0.86	0.94	0.86	0.83
(95% CI)	(0.93–0.99)	(0.85–0.93)	(0.79–0.89)	(0.95–0.99)	(0.86–0.93)	(0.86–0.93)	(0.94–0.97)	(0.86–0.91)	(0.42–0.48)	(0.95–0.99)	(0.85–0.94)	(0.89–0.96)	(0.91–0.98)	(0.80–0.91)	(0.80–0.91)	(0.93–0.96)	(0.83–0.88)	(0.81–0.86)
NPV	0.96	0.97	0.97	0.93	0.94	0.93	0.82	0.84	0.92	0.95	0.95	0.96	0.94	0.94	0.94	0.64	0.70	0.71
(95% CI)	(0.95–0.97)	(0.96–0.98)	(0.96–0.98)	(0.91–0.94)	(0.92–0.95)	(0.92–0.95)	(0.79–0.84)	(0.81–0.86)	(0.90–0.94)	(0.93–0.96)	(0.94–0.96)	(0.94–0.97)	(0.92–0.95)	(0.93–0.96)	(0.93–0.96)	(0.60–0.68)	(0.66–0.74)	(0.67–0.74)

* Includes agreement of both users and nonusers.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; DDD, defined daily dose; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

4. Discussion

This study demonstrates high agreement between self-reported use of CHD medications and pharmacy dispensing data among participants with CHD in the seventh wave of the Tromsø Study. High PPV was shown for all medications, especially when using a fixed-time window. This indicates that participants reporting use of such medications can be presumed to be actual medication-users. Sensitivity and specificity was also found to be high for the investigated medication classes. This is in accordance with previous studies [4-7,9,10,12,14–16].

Negative predictive values were also high for most medication classes, showing that almost all who do not report use of CHD medications are nonusers in NorPD as well. Lower NPVs for statins and ASA suggest that among participants not reporting use of these medications, some have been dispensed such medications. It is possible that these participants do not actually use statins or ASA, but it is more likely that they have forgotten to report them in the questionnaire, thereby being misclassified as nonusers according to self-report. Predictive values are affected by prevalence and the high prevalence of use in our study population contributes to the high PPVs.

In addition to lower NPV, ASA had a lower kappa-value, as more participants were classified as ASA-users by NorPD, and not by Tromsø 7. This was particularly clear using fixed-time window, where 10.7% of the participants were defined as medication-users in NorPD only, while 2.6% were defined as users only in Tromsø 7. Unlike for antihypertensive drugs and LLDs, we could only include those who specified an ASA brand name, and we would lose users who wrote "blood-thinning medication". As this could represent any antithrombotic drug, we could not include these as ASA-users. We did include answers to a prespecified question about use of low-dose ASA, but this question was conditional on a positive answer to a previous question ("Have you used analgesics and anti-inflammatory medication regularly in the past year?"). So, ASA-users did not have the same opportunity as LLD-/antihypertensive drug-users to report their use, leading to a likely underestimated agreement for ASA.

Like ASA, statins had lower agreement and NPV than the other medication classes. However, the values for all LLDs combined were higher than for statins alone, especially when using fixed-time window. Many LLD-users remember that they use LLDs, but might not report which type. This again underlines the importance of including the prespecified question about LLD-use in addition to the open-ended question when evaluating use of statins. Interestingly, LLDs is the only medication class with a higher proportion of users defined in Tromsø 7 than in NorPD. The number of users defined by Tromsø 7 alone is lower when using a fixed-time window of 365 days, indicating lower adherence among LLD-users.

The lowest sensitivity was found for thiazides, indicating that the Tromsø 7 questionnaire does not identify all thiazide-users. Only the open-ended question was used to define thiazide-users, and we are therefore dependent on the participants being specific when listing their medications. In Norway, thiazides are usually sold as part of a combination product with another antihypertensive drug. Self-reported use of combination products can be misclassified as single active substances. The thiazide is usually mentioned at the end of a brand name, e.g. "candesartan hydrochlorothiazide", leaving it easy to forget, and resulting in lower sensitivity for thiazides.

The structure of the questions in a questionnaire can affect how a participant reports medication use [25]. A study by Klungel et al. [2] compared questions about medications for prespecified conditions with open-ended question and concluded that prespecified indication alternatives gave higher recall sensitivity. However, the open-ended question and the question with prespecified indications did not ask about the same medication type. Combining the information from different types of questions should yield higher prevalence of medication use [25]. In our study, we combined prespecified questions and an open-ended question. Thereby we could capture participants who forgot to list some of their medicines in the open-ended question and participants who use antihypertensive drugs and LLDs without understanding exactly what the medication is for. The two questions might lead to different responses as the prespecified questions ask about current medication use, while the open-ended one asks about regular use in the last four weeks. As CHD medications are used chronically, it is reasonable to assume that both questions would capture the participants' recent use of these medications.

It is not possible to define current use in a prescription registry in the same way as in a questionnaire. NorPD states that a medication was dispensed at a certain date and amount, but not if, when or how the medication was taken. Two main methods have been used when assessing current medication use in pharmacy records: fixed-time windows (also called fixed look-back periods) and legend-time (also called legend-duration or medication-on-hand) [18]. As there is no consensus on the best method for defining current medication use in pharmacy records, it has been recommended to compare different approaches [18]. We chose to use both fixed-time window and legend-time methods to define current medication use in NorPD. A fixed-time window of 180 days was chosen because a typical dispensing in Norway covers around 90 days of use, and we added another 90 days to account for poor adherence and stockpiling. For the same reason we added 10% to the units and DDDs before calculating whether the dispensed duration would last to the index day when using the legend-time method [2,12,15,17]. The sensitivity analyses suggest that this was satisfactory.

Using one unit compared with one DDD to calculate legend duration gave similar results for most of the medication classes. The sensitivity was slightly higher when using DDDs, while using units generally gave higher agreement, specificity and PPV. The differences were largest for beta-blockers. This indicates that the DDD for beta-blockers is higher than the most commonly prescribed dose of beta-blockers in Norway. As most of the medications used for secondary prevention of CHD are used as one unit daily, this appears to be a better estimate for the prescribed daily dosage than DDD. The only exception among the medication classes was calcium-channel blockers, where the DDD gave slightly higher agreement, sensitivity and PPV than the unit. This is not unexpected, as some calcium-channel blockers are recommended to be taken more than once a day.

We used NorPD as the reference standard in calculating our validity measures. NorPD can be considered more reliable than self-report as the registry has complete coverage of dispensed medications used for secondary prevention of CHD. These medications are also not available over-the-counter in Norway. Using dispensing data as the reference standard is common in validation studies [4–6,9,10]. However, the choice of definition matters, and careful considerations are needed when choosing fixed-time or legend-time, and dosage unit or DDD as unit of use. We found that for CHD medications used chronically, a fixed-time window of 180 days gave the best results with higher values of both percent agreement and kappa as well as higher specificity and PPV for all medications. Though sensitivity and NPV was higher for most medications when using the legend-time methods, the differences from fixed-time window were small. The fixed-time window is also more easily applicable than the legend-time method. Overall, using a fixed-time window could be recommended for most studies investigating use of these medications. For other medication classes this might be different.

5. Conclusion

Self-reported information on current use of medications for secondary prevention of coronary heart disease collected with a questionnaire combining prespecified and open-ended questions shows high validity compared with pharmacy dispensing data. Though a combination with dispensing data is preferable, this questionnaire provides a sufficiently accurate classification of such medication exposure should prescription data be unavailable.

Validity and agreement measures varied depending on the definition of medication use in NorPD. For CHD medications, using a fixed-time window gave better results than the legend-time methods. However, this may vary depending on medication class, setting and data source.

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CRediT authorship contribution statement

Elisabeth Pedersen: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Kieu Nhi Lise Truong:** Conceptualization, Formal analysis, Writing - review & editing. **Beate Hennie Garcia:** Conceptualization, Writing - review & editing. **Kjell H. Halvorsen:** Writing - review & editing. **Kristian Svendsen:** Formal analysis, Writing - review & editing. **Anne Elise Eggen:** Writing - review & editing. **Marit Waaseth:** Conceptualization, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.02.015.

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Supplementary material

Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data

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Content:

Supplementary tables A.1-A.3

Table A.1: Sensitivity analysis comparing self-reported medication use in the Tromsø 7 questionnaire with dispensed prescriptions in NorPD, using a fixed-time window of 90 and 365 days to define users in NorPD (n = 1483)

Medication class	Observed agreement* n (%)		Kappa (95% CI)		Both n (%)		Tromsø 7 only n (%)		NorPD only n (%)		Neither n (%)		Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)	
90 days																				
Antihypertensive drugs	1265	(85.3)	0.67	(0.63-0.71)	896	(60.4)	173	(11.7)	45	(3.0)	369	(24.9)	0.95	(0.94-0.97)	0.68	(0.64-0.72)	0.84	(0.81-0.86)	0.89	(0.86-0.92)
ACE-inhibitor	1402	(94.5)	0.77	(0.72-0.82)	163	(11.0)	42	(2.8)	39	(2.6)	1239	(83.6)	0.81	(0.74-0.86)	0.97	(0.96-0.98)	0.80	(0.73-0.85)	0.97	(0.96-0.98)
ARB	1345	(90.7)	0.73	(0.69-0.77)	262	(17.7)	64	(4.3)	74	(5.0)	1083	(73.0)	0.78	(0.73-0.82)	0.94	(0.93-0.96)	0.80	(0.76-0.85)	0.94	(0.92-0.95)
Beta-blocker	1227	(82.7)	0.65	(0.61-0.69)	537	(36.2)	133	(9.0)	123	(8.3)	690	(46.5)	0.81	(0.78-0.84)	0.84	(0.81-0.86)	0.80	(0.77-0.83)	0.85	(0.82-0.87)
CCB	1388	(93.6)	0.76	(0.71-0.80)	185	(12.5)	46	(3.1)	49	(3.3)	1203	(81.1)	0.79	(0.73-0.84)	0.96	(0.95-0.97)	0.80	(0.74-0.85)	0.96	(0.95-0.97)
Thiazide	1378	(92.9)	0.68	(0.62-0.74)	135	(9.1)	36	(2.4)	69	(4.7)	1243	(83.8)	0.66	(0.59-0.73)	0.97	(0.96-0.98)	0.79	(0.72-0.85)	0.95	(0.93-0.96)
Lipid-lowering drugs	1172	(79.0)	0.55	(0.51-0.59)	835	(56.3)	298	(20.1)	13	(0.9)	337	(22.7)	0.99	(0.97-0.99)	0.53	(0.49-0.57)	0.74	(0.71-0.76)	0.96	(0.94-0.98)
Statin	1114	(75.1)	0.49	(0.45-0.54)	674	(45.5)	216	(14.6)	153	(10.3)	440	(29.7)	0.82	(0.79-0.84)	0.67	(0.63-0.71)	0.76	(0.73-0.79)	0.74	(0.70-0.78)
Acetylsalicylic acid	1127	(76.0)	0.49	(0.45-0.54)	748	(50.4)	232	(15.6)	124	(8.4)	379	(25.6)	0.86	(0.83-0.88)	0.62	(0.58-0.66)	0.76	(0.74-0.79)	0.75	(0.71-0.79)
365 days																				
Antihypertensive drugs	1384	(93.3)	0.83	(0.79-0.86)	1050	(70.8)	19	(1.3)	80	(5.4)	334	(22.5)	0.93	(0.91-0.94)	0.95	(0.92-0.97)	0.98	(0.97-0.99)	0.81	(0.77-0.84)

ACE-inhibitor	1423	(96.0)	0.85	(0.81-0.88)	200	(13.5)	5	(0.3)	55	(3.7)	1223	(82.5)	0.78	(0.73-0.83)	1.00	(0.99-1.00)	0.98	(0.94-0.99)	0.96	(0.94-0.97)
ARB	1387	(93.5)	0.83	(0.80-0.86)	323	(21.8)	3	(0.2)	93	(6.3)	1064	(71.8)	0.78	(0.73-0.82)	1.00	(0.99-1.00)	0.99	(0.97-1.00)	0.92	(0.90-0.93)
Beta-blocker	1296	(87.4)	0.75	(0.72-0.78)	666	(44.9)	4	(0.3)	183	(12.3)	630	(42.5)	0.78	(0.76-0.81)	0.99	(0.98-1.00)	0.99	(0.98-1.00)	0.78	(0.74-0.80)
CCB	1396	(94.1)	0.81	(0.77-0.85)	230	(15.5)	1	(0.1)	86	(5.8)	1166	(78.6)	0.73	(0.68-0.78)	1.00	(1.00-1.00)	1.00	(0.97-1.00)	0.93	(0.92-0.94)
Thiazide	1389	(93.7)	0.75	(0.70-0.80)	169	(11.4)	2	(0.1)	92	(6.2)	1220	(82.3)	0.65	(0.59-0.71)	1.00	(0.99-1.00)	0.99	(0.95-1.00)	0.93	(0.91-0.94)
Lipid-lowering drugs	1384	(93.3)	0.81	(0.78-0.85)	1091	(73.6)	42	(2.8)	57	(3.8)	293	(19.8)	0.95	(0.94-0.96)	0.88	(0.83-0.91)	0.96	(0.95-0.97)	0.84	(0.79-0.87)
Statin	1215	(81.9)	0.60	(0.56-0.64)	879	(59.3)	11	(0.7)	257	(17.3)	336	(22.7)	0.77	(0.75-0.80)	0.97	(0.94-0.98)	0.99	(0.98-0.99)	0.57	(0.53-0.61)
Acetylsalicylic acid	1284	(86.6)	0.67	(0.63-0.71)	968	(65.3)	12	(0.8)	187	(12.6)	316	(21.3)	0.84	(0.82-0.86)	0.96	(0.94-0.98)	0.99	(0.98-0.99)	0.63	(0.58-0.67)

*Includes agreement of both users and non-users

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

Table A.2: Sensitivity analysis comparing self-reported medication use in the Tromsø 7 questionnaire with dispensed prescriptions in NorPD, using legend-time method with one dosage unit a day (+0% and +20%) to define users in NorPD (n = 1483)

Medication class	Observed agreement* n (%)	Kappa (95% CI)	Both n (%)	Tromsø 7 only n (%)	NorPD only n (%)	Neither n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
No extra dosage units added										
Antihypertensive drugs	1334 (90.0)	0.76 (0.72-0.80)	966 (65.1)	103 (7.0)	46 (3.1)	368 (24.8)	0.96 (0.94-0.97)	0.78 (0.74-0.82)	0.90 (0.88-0.92)	0.89 (0.85-0.92)
ACE-inhibitor	1416 (95.5)	0.82 (0.77-0.86)	177 (11.9)	28 (1.9)	39 (2.6)	1239 (83.6)	0.82 (0.76-0.87)	0.98 (0.97-0.99)	0.86 (0.81-0.91)	0.97 (0.96-0.98)

ARB	1366	(92.1)	0.78	(0.74-0.82)	282	(19.0)	44	(3.0)	73	(4.9)	1084	(73.1)	0.79	(0.75-0.83)	0.96	(0.95-0.97)	0.87	(0.82-0.90)	0.94	(0.92-0.95)
Beta-blocker	1257	(84.8)	0.69	(0.66-0.73)	571	(38.5)	99	(6.7)	127	(8.6)	686	(46.3)	0.82	(0.79-0.85)	0.87	(0.85-0.90)	0.85	(0.82-0.88)	0.84	(0.82-0.87)
CCB	1398	(94.3)	0.79	(0.75-0.83)	202	(13.6)	29	(2.0)	56	(3.8)	1196	(80.7)	0.78	(0.73-0.83)	0.98	(0.97-0.98)	0.87	(0.82-0.91)	0.96	(0.94-0.97)
Thiazide	1384	(93.3)	0.71	(0.65-0.76)	144	(9.7)	27	(1.8)	72	(4.9)	1240	(83.6)	0.67	(0.60-0.73)	0.98	(0.97-0.99)	0.84	(0.78-0.89)	0.95	(0.93-0.96)
Lipid-lowering drugs	1240	(83.6)	0.63	(0.58-0.67)	905	(61.0)	228	(15.4)	15	(1.0)	335	(22.6)	0.98	(0.97-0.99)	0.60	(0.55-0.64)	0.80	(0.77-0.82)	0.96	(0.93-0.98)
Statin	1153	(77.8)	0.54	(0.49-0.58)	728	(49.1)	162	(10.9)	168	(11.3)	425	(28.7)	0.81	(0.79-0.84)	0.72	(0.69-0.76)	0.82	(0.79-0.84)	0.72	(0.68-0.75)
Acetylsalicylic acid	1180	(79.6)	0.55	(0.51-0.60)	809	(54.6)	171	(11.5)	132	(8.9)	371	(25.0)	0.86	(0.84-0.88)	0.69	(0.64-0.72)	0.83	(0.80-0.85)	0.74	(0.70-0.78)
20% extra dosage units added																				
Antihypertensive drugs	1362	(91.8)	0.80	(0.77-0.83)	1000	(67.4)	69	(4.7)	52	(3.5)	362	(24.4)	0.95	(0.94-0.96)	0.84	(0.80-0.87)	0.94	(0.92-0.95)	0.87	(0.84-0.90)
ACE-inhibitor	1426	(96.2)	0.85	(0.81-0.89)	189	(12.7)	16	(1.1)	41	(2.8)	1237	(83.4)	0.82	(0.77-0.87)	0.99	(0.98-0.99)	0.92	(0.87-0.95)	0.97	(0.96-0.98)
ARB	1386	(93.5)	0.82	(0.79-0.86)	307	(20.7)	19	(1.3)	78	(5.3)	1079	(72.8)	0.80	(0.75-0.84)	0.98	(0.97-0.99)	0.94	(0.91-0.96)	0.93	(0.92-0.95)
Beta-blocker	1291	(87.1)	0.74	(0.71-0.78)	614	(41.4)	56	(3.8)	136	(9.2)	677	(45.7)	0.82	(0.79-0.85)	0.92	(0.90-0.94)	0.92	(0.89-0.94)	0.83	(0.81-0.86)
CCB	1406	(94.8)	0.82	(0.78-0.86)	214	(14.4)	17	(1.2)	60	(4.1)	1192	(80.4)	0.78	(0.73-0.83)	0.99	(0.98-0.99)	0.93	(0.88-0.96)	0.95	(0.94-0.96)
Thiazide	1391	(93.8)	0.74	(0.69-0.79)	155	(10.5)	16	(1.1)	76	(5.1)	1236	(83.4)	0.67	(0.61-0.73)	0.99	(0.98-0.99)	0.91	(0.85-0.94)	0.94	(0.93-0.95)
Lipid-lowering drugs	1299	(87.6)	0.70	(0.66-0.74)	968	(65.3)	165	(11.1)	19	(1.3)	331	(22.3)	0.98	(0.97-0.99)	0.67	(0.62-0.71)	0.85	(0.83-0.87)	0.95	(0.92-0.97)
Statin	1188	(80.1)	0.58	(0.53-0.62)	779	(52.5)	111	(7.5)	184	(12.4)	409	(27.6)	0.81	(0.78-0.83)	0.79	(0.75-0.82)	0.88	(0.85-0.90)	0.69	(0.65-0.73)

Acetylsalicylic acid	1238	(83.5)	0.62	(0.58-0.67)	880	(59.3)	100	(6.7)	145	(9.8)	358	(24.1)	0.86	(0.84-0.88)	0.78	(0.74-0.82)	0.90	(0.88-0.92)	0.71	(0.67-0.75)

*Includes agreement of both users and non-users

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

Table A.3: Sensitivity analysis comparing self-reported medication use in the Tromsø 7 questionnaire with dispensed prescriptions in NorPD, using legend-time method with one DDD a day (+0% and +20%) to define users in NorPD (n = 1483)

Medication class	Observed agreement* n (%)		Kappa (95% CI)		Both n (%)		Tromsø 7 only n (%)		NorPD only n (%)		Neither n (%)		Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)	
No extra DDDs added																				
Antihypertensive drugs	1202	(81.2)	0.60	(0.56-0.64)	816	(55.0)	253	(17.1)	28	(1.9)	386	(26.0)	0.97	(0.95-0.98)	0.60	(0.57-0.64)	0.76	(0.74-0.79)	0.93	(0.90-0.95)
ACE-inhibitor	1405	(94.7)	0.78	(0.73-0.83)	166	(11.2)	39	(2.6)	39	(2.6)	1239	(83.6)	0.81	(0.75-0.86)	0.97	(0.96-0.98)	0.81	(0.75-0.86)	0.97	(0.96-0.98)
ARB	1365	(92.0)	0.78	(0.74-0.81)	283	(19.1)	43	(2.9)	75	(5.1)	1082	(73.0)	0.79	(0.74-0.83)	0.96	(0.95-0.97)	0.87	(0.83-0.90)	0.94	(0.92-0.95)
Beta-blocker	1048	(70.7)	0.38	(0.34-0.43)	295	(19.9)	375	(25.3)	60	(4.1)	753	(50.8)	0.83	(0.79-0.87)	0.67	(0.64-0.70)	0.44	(0.40-0.48)	0.93	(0.91-0.94)
CCB	1408	(94.9)	0.82	(0.78-0.86)	208	(14.0)	23	(1.6)	52	(3.5)	1200	(80.9)	0.80	(0.75-0.85)	0.98	(0.97-0.99)	0.90	(0.85-0.94)	0.96	(0.95-0.97)
Thiazide	1383	(93.3)	0.70	(0.65-0.76)	143	(9.6)	28	(1.9)	72	(4.9)	1240	(83.6)	0.67	(0.60-0.73)	0.98	(0.97-0.99)	0.84	(0.77-0.89)	0.95	(0.93-0.96)
Lipid-lowering drugs	1220	(82.3)	0.60	(0.56-0.64)	887	(59.8)	246	(16.6)	17	(1.2)	333	(22.5)	0.98	(0.97-0.99)	0.58	(0.53-0.62)	0.78	(0.76-0.81)	0.95	(0.92-0.97)
Statin	1151	(77.6)	0.53	(0.49-0.58)	724	(48.8)	166	(11.2)	166	(11.2)	427	(28.8)	0.81	(0.79-0.84)	0.72	(0.68-0.76)	0.81	(0.79-0.84)	0.72	(0.68-0.76)
Acetylsalicylic acid	1180	(79.6)	0.55	(0.51-0.60)	809	(54.6)	171	(11.5)	132	(8.9)	371	(25.0)	0.86	(0.84-0.88)	0.69	(0.64-0.72)	0.83	(0.80-0.85)	0.74	(0.70-0.78)
20% extra DDDs added																				
Antihypertensive drugs	1244	(83.9)	0.65	(0.61-0.69)	860	(58.0)	209	(14.1)	30	(2.0)	384	(25.9)	0.97	(0.95-0.98)	0.65	(0.61-0.69)	0.80	(0.78-0.83)	0.93	(0.90-0.95)
ACE-inhibitor	1417	(95.6)	0.82	(0.78-0.86)	181	(12.2)	24	(1.6)	42	(2.8)	1236	(83.4)	0.81	(0.75-0.86)	0.98	(0.97-0.99)	0.88	(0.83-0.92)	0.97	(0.96-0.98)
ARB	1382	(93.2)	0.81	(0.78-0.85)	304	(20.5)	22	(1.5)	79	(5.3)	1078	(72.7)	0.79	(0.75-0.83)	0.98	(0.97-0.99)	0.93	(0.90-0.96)	0.93	(0.92-0.95)

Beta-blocker	1071	(72.2)	0.42	(0.38-0.46)	327	(22.1)	343	(23.1)	69	(4.7)	744	(50.2)	0.83	(0.78-0.86)	0.68	(0.66-0.71)	0.49	(0.45-0.53)	0.92	(0.89-0.93)
CCB	1412	(95.2)	0.83	(0.79-0.87)	217	(14.6)	14	(0.9)	57	(3.8)	1195	(80.6)	0.79	(0.74-0.84)	0.99	(0.98-0.99)	0.94	(0.90-0.97)	0.95	(0.94-0.97)
Thiazide	1390	(93.7)	0.73	(0.68-0.78)	154	(10.4)	17	(1.2)	76	(5.1)	1236	(83.4)	0.67	(0.60-0.73)	0.99	(0.98-0.99)	0.90	(0.84-0.94)	0.94	(0.93-0.95)
Lipid-lowering drugs	1259	(84.9)	0.65	(0.61-0.69)	927	(62.5)	206	(13.9)	18	(1.2)	332	(22.4)	0.98	(0.97-0.99)	0.62	(0.57-0.66)	0.82	(0.79-0.84)	0.95	(0.92-0.97)
Statin	1172	(79.0)	0.56	(0.52-0.60)	755	(50.9)	135	(9.1)	176	(11.9)	417	(28.1)	0.81	(0.78-0.84)	0.76	(0.72-0.79)	0.85	(0.82-0.87)	0.70	(0.66-0.74)
Acetylsalicylic acid	1238	(83.5)	0.62	(0.58-0.67)	880	(59.3)	100	(6.7)	145	(9.8)	358	(24.1)	0.86	(0.84-0.88)	0.78	(0.74-0.82)	0.90	(0.88-0.92)	0.71	(0.67-0.75)

*Includes agreement of both users and non-users

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; NorPD, Norwegian Prescription Database; NPV, negative predictive value; PPV, positive predictive value

Paper III

Medication adherence among persons with coronary heart disease and associations with blood pressure and low-density-lipoprotein-cholesterol

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Abstract

Purpose: To describe medication adherence to lipid-lowering drugs (LLDs), antihypertensive drugs and acetylsalicylic acid (ASA) among persons with coronary heart disease (CHD) and explore its association with low-density-lipoprotein (LDL)-cholesterol, and systolic and diastolic blood pressure.

Methods: Based on record linkage between the seventh wave of the Tromsø study and the Norwegian Prescription Database, medication adherence was calculated as proportion of days covered (PDC) for persistent prevalent users in the time-period of 365 days before the attendance date. Multivariable linear regression models were used to assess the association between systolic and diastolic blood pressure and medication nonadherence to antihypertensive drugs, age, sex, lifestyle, body mass index (BMI), current and previous diabetes and between LDL-cholesterol and medication nonadherence to LLDs, age, sex, lifestyle, BMI, current and previous diabetes.

Results: Mean PDC was 0.94 for LLDs and antihypertensive drugs and 0.97 for ASA. Among persons with PDC ≥0.80 for LLDs, 12.0% had an LDL-cholesterol <1.8 mmol/L. Blood pressure <140/90 mmHg (<140/80 mmHg if diabetes patient) was reached by 55.1% of those with a PDC ≥0.80 for antihypertensive drugs. Adherence to LLDs was associated with lower LDL-cholesterol, while neither systolic nor diastolic blood pressure were associated with adherence to antihypertensive drugs.

Conclusion: Adherence to antihypertensive drugs, LLDs and ASA among persons with CHD was high despite low achievement of treatment goals for blood pressure and LDL-cholesterol. There was a statistically significant association between adherence to LLDs and LDL-cholesterol, but not between adherence to antihypertensive drugs and blood pressure.

Keywords: medication adherence, coronary heart disease, lipid-lowering drugs, antihypertensive drugs, acetylsalicylic acid.

Introduction

Adherence to medications for secondary prevention of coronary heart disease (CHD) is important to achieve full effect of lipid-lowering drugs (LLDs), antihypertensive drugs and low-dose acetylsalicylic acid (ASA) and thereby to avoid new cardiovascular events [1-4].

Lowering low-density-lipoprotein (LDL)-cholesterol and blood pressure reduces the risk of further morbidity and mortality of coronary heart disease [5, 6]. European guidelines for prevention of cardiovascular disease have recommended that patients with established CHD should have a blood pressure of <140/90 mmHg (<140/80 mmHg in patients with diabetes) and an LDL-cholesterol of <1.8 mmol/l (<70 mg/dL) [7, 8]. In the more recent guidelines concerning management of chronic coronary syndromes and those concerning hypercholesterolemia, the recommendations for persons with a very high risk of new coronary events are now further reduced to an LDL-cholesterol reduction of ≥50% from baseline and an LDL-cholesterol goal of <1.4 mmol/L (<55 mg/dL) [9, 10]. Risk factor control among persons with CHD is found to be suboptimal, also in population-based studies [11-14]. Achievement of the treatment goal for LDL-cholesterol is particularly low. Suboptimal medication adherence has been suggested as a possible explanation for the poor treatment goal achievement. Several studies have found an association between being adherent and achieving LDL-cholesterol or blood pressure control [15-19].

Adherence to long-term therapies is generally found to be as low as 50% [20]. Although some studies have found slightly higher adherence to medications used for secondary prevention of CHD, there is still potential for improvement [1, 17, 21]. Being adherent is normally defined as having a measure of adherence (e.g. proportion of days covered (PDC) or medication possession ratio (MPR)) of ≥80% [20]. Although this cut-off is considered arbitrary, some

studies have found that for medications used for cardiovascular diseases, a medication adherence of ≥80% is associated with fewer adverse coronary events [4].

The medication adherence process can be divided into three separate phases: initiation, implementation and discontinuation. Initiation determines when the first dose is taken, implementation indicates to which extent patients' actual dosing corresponds to the prescribed regiment and is often measured as a proportion, while discontinuation marks the last dose taken and thus the end of treatment [22]. Persistence is defined as the time between initiation and discontinuation.

Few studies have assessed the association between medication adherence and LDL-cholesterol and systolic and diastolic blood pressure as continuous measures. Adherence to LLDs, antihypertensive drugs and ASA among persistent prevalent medication users with CHD has also not been properly described.

This study aims to describe medication adherence to LLDs, antihypertensive drugs and ASA among persons with CHD, focusing on the implementation phase of the adherence process, and explore its association with LDL-cholesterol serum concentrations, and systolic and diastolic blood pressure.

Methods

Data sources

The data for this study was retrieved from the seventh wave of the Tromsø Study (Tromsø 7, conducted in 2015-6) and the Norwegian Prescription Database (NorPD).

The Tromsø Study is a Norwegian population-based epidemiological health study that has been conducted seven times since 1974. The population of the Tromsø Study consists of inhabitants in the municipality of Tromsø in North Norway, a university town with

approximately 73 000 inhabitants in 2016. Tromsø 7 invited all inhabitants in the municipality aged 40 years or older (n = 32,591). Attendance rate was 65% (n = 21,083).

Data collection includes questionnaires, interviews, biological sampling, and clinical examinations from where we extracted blood pressure and anthropometric measurements (height and weight), LDL-cholesterol values, and self-reported diseases, lifestyle, and demographic information.

Data from Tromsø 7 was linked with NorPD data using the unique national identity number assigned to all citizens in Norway. NorPD contains information on all prescriptions dispensed to individuals from Norwegian pharmacies. Medications given at hospitals, nursing homes, or over-the-counter is not included. We extracted the following variables: date of dispensing and information on medications dispensed, including Anatomical Therapeutic Chemical (ATC) code [23] and number of dosage units dispensed. Prescribed daily dosage is not available in NorPD and we therefore assumed a daily dosage of one dosage unit (e.g., tablet or capsule).

Study population

The study population consisted of participants reporting established CHD (n=1483), defined as previous myocardial infarction, present or previous angina pectoris, previous percutaneous coronary intervention or coronary artery bypass graft surgery.

Medications included

From NorPD, we included use of medications for secondary prevention of CHD based on the prevailing European clinical guidelines in 2015/2016. This included ASA, LLDs (mainly statins) and antihypertensive drugs (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), thiazides and other antihypertensives) [7]. ATC-codes for the medications included can be found in Online Resource 1. The number of participants using the different medication groups and subgroups can be found in Fig. 1 and Online Resource 2.

Adherence measurement

We calculated adherence to medication use as proportion of days covered (PDC), calculated as a continuous multiple-interval measure of medication availability (CMA) 7 in the R-package AdhereR [24]. CMA7 is defined as "number of gap days for all event intervals extracted from the total time interval; (accounting for carry over from before the observation window and within the observation window, and excluding the supply left at the observation window end)" [24, 25]. The observation window was set from 365 days before the attendance date in Tromsø 7 until the attendance date (see Fig. 2). The follow-up window was set from the 1st of January 2004 until the 31st of December 2016 in order to utilize all available data from NorPD. The medications supplied before the beginning of the observation window could then be carried over into the observation window if the days supplied extended into this period. Medication supplied from prescriptions filled before the end of the previous supplies were also carried forward to after the end of the previous days supplied. This was only done within the same 5th level ATC-code (chemical substance level) to avoid overestimating medication supplies in connection to switches of medications within the same medication group.

Adherence calculations were done for persistent prevalent users, defined as participants who had used the medications from before the start of the observation window and had supplies available to cover days within 180 days before attendance in Tromsø 7. Incident and nonpersistent users were excluded (see Fig. 1 and 2). Incident users were defined as participants who had not filled any prescriptions for the relevant medications within 365 days before the first prescription in the observation window. These were excluded because they had too few dispensing of the relevant medications before attending Tromsø 7 for the calculated PDC to be reliable. Adherence estimations during short time intervals is found to be imprecise and it is therefore recommended to calculate PDC only when the observation

window is long enough to last at least three dispensings or over 9 months [25]. In Norway, a typical dispensing of LLDs, antihypertensive drugs or ASA lasts about three months, hence four dispensings should cover one year. Nonpersistent users were defined as those not having any days covered with the relevant medications within 180 days before the attendance date. These were excluded from our analyses because discontinuation is a different step in the adherence process and those who discontinue treatment could therefore be different than those who have poor implementation [22]. In a previous study we have also considered those without medications dispensed within 180 days before attending Tromsø 7 as not being medication users at the time of attendance [26]. Our focus in the current study was thereby on the implementation phase within the adherence taxonomy [22].

For users of several antihypertensive drugs and LLDs, a day was considered covered when at least one of the medications was available [19, 27]. See Fig. 1 for an overview of medication users per medication group, for subgroups see Online Resource 2.

Measurement of LDL-cholesterol and blood pressure

In Tromsø 7, blood pressure was measured by trained personnel using a digital automated device (Dinamap ProCare 300 monitor, GE Healthcare, Norway). Three measurements were taken with one-minute intervals and after two minutes of seated rest [12]. In the analyses, we used the mean of the two final measurements, except if the third measurement was missing (n = 2), then we only used the second measurement. If both the second and third measurement was missing (n = 1), we used the first measurement. Three participants did not have any blood pressure measurements registered and were excluded from the analyses examining blood pressure. Achieving the treatment goal for blood pressure was defined as having a blood pressure <140/90 mmHg (<140/80 mmHg in those with diabetes) [7].

LDL-cholesterol was collected and analysed by trained personnel using enzymatic colorimetric methods with commercial kits on a Cobas 8000 c702 (Roche Diagnostics GmbH,

Mannheim, Germany) from non-fasting venous blood samples. The analysis was performed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway (ISO certification NS-EN ISO 15189:2012) [12]. Eleven participants did not have any LDL-cholesterol measurements registered and were excluded from the analysis of LDL-cholesterol. The treatment goal for LDL-cholesterol was set to <1.8 mmol/L based on the European guidelines from 2012 which were the prevailing guidelines at the time of Tromsø 7 [7].

Covariates

Weight and height were measured with light clothing and no shoes to the nearest 0.1 kilograms and 0.1 centimetres using the Jenix DS-102 height and weight scale (DongSahn Jenix, Seoul, Korea). We calculated body mass index (BMI) as weight in kilograms divided by height in metres squared.

We collected variables concerning current or previous diabetes and lifestyle from questionnaires in Tromsø 7. Having a diagnosis of diabetes was defined as answering "yes, currently" or "previously, not now" when asked "Have you ever had, or do you have diabetes?" (answering options "no", "yes, currently" and "previously, not now") or reporting current use of antidiabetic drugs, either by reporting a brand name of an antidiabetic drug when asked to state the name of all medicines used regularly during the last 4 weeks, or checking off "now" when asked "Do you use or have you used tablets for diabetes/insulin?". Participants were considered not having diabetes if they did not reply to whether they had diabetes and did not report using any antidiabetic drug.

Two variables summarizing lifestyle were obtained using multidimensional scaling, computed with the R package vegan, applied to a multivariate dataset including variables concerning self-reported smoking, alcohol use, diet and physical activity. For more information about these variables, see Online Resource 3.

Statistical analysis

Descriptive statistics are presented as proportions and means with standard deviation (sd). We applied three multivariable linear regression models to assess the association between systolic and diastolic blood pressure and medication nonadherence to antihypertensive drugs, age, sex, lifestyle, BMI, current and previous diabetes (model i & ii) and between LDL-cholesterol and medication nonadherence to LLDs, age, sex, lifestyle, BMI, current and previous diabetes (model iii). Medication nonadherence was assessed as the adherence variables had to be reversed and log-transformed (1.1 – log(PDC)) in these analyses (skewness in variables). The analyses were done as complete case analyses, hence excluding participants with missing values in the relevant variables. Significance level was set to 5%.

The analyses were conducted using R (R Core Team (2021), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics of North Norway (2015/1775) and had an approved Data Protection Impact Assessment (DPIA) from UiT The Arctic University of Norway. All participants in the Tromsø Study have given written informed consent for their data to be used in research.

Results

Participants defined as persistent prevalent medication users were 1003 for LLDs, 1046 for antihypertensive drugs and 1042 for ASA (Fig. 1). The number of participants that had been dispensed prescriptions for all three medication groups was 701, while 113 participants had not had any dispensed prescriptions for any of three. Characteristics of the total study population and users of each of the medication groups are shown in Table 1.

Medication adherence was high, with a mean PDC of ≥0.94 for all medication groups and subgroups (Table 2). The distribution of PDC in all medication groups is shown in Fig. 3.

Treatment goals for both systolic and diastolic blood pressure (<140/90 mmHg, <140/80 mmHg if diabetic) was reached for 54.7% of the antihypertensive drug users. The treatment goal for systolic blood pressure was reached by 56.8%, while 90.9% reached the goal for diastolic blood pressure. The proportion of participants reaching the blood pressure goal among participants with a PDC ≥0.80 (n = 963) was 55.1% compared to 49.4% among those with PDC <0.80 (n=83).

For the LLD-users, the proportion reaching the treatment goal for LDL-cholesterol (<1.8 mmol/L or <70 mg/dL) was 11.2%. The proportion of participants reaching the treatment goal among participants with a PDC ≥ 0.80 (n = 884) was 12.0% compared to 5.0% among those with a PDC < 0.80 (n = 119).

The regression models (Table 3) show that an increased systolic blood pressure was significantly associated with higher age (β 0.31, p<.001), while an increased diastolic blood pressure was significantly associated with lower age (β -0.14, p<.001), male sex (β 0.09, p=.009) and lifestyle (β 0.10, p=.008). None of the blood pressure measurements were significantly associated with adherence to antihypertensive drug use. An increase in LDL cholesterol was significantly associated with nonadherence to LLDs (β 0.12, p<.001), female sex (β -0.12, p<.001), lifestyle (β 0.14, p<.001) and current diabetes (β -0.09, p=.009).

The regression models indicated that the predictors explained 9.9% of the variance in systolic blood pressure (adjusted R^2 = 0.099, F(8,930)= 13.91, p<.001), 6.3% of the variance in diastolic blood pressure (adjusted R^2 = 0.063, F(8,930)= 8.84, p<.001) and 4.2% of the variance in LDL-cholesterol (adjusted R^2 = 0.042, F(8,900)= 5.96, p<.001).

Discussion

In this study we have identified a high medication adherence to antihypertensive drugs, lipid-lowering drugs and acetylsalicylic acid among persons with CHD. Despite the high adherence, achievement of treatment goals for blood pressure and LDL-cholesterol was low. From the regression models, we found that adherence to LLDs was significantly associated with a lower LDL-cholesterol, but no significant association was identified between adherence to antihypertensive drugs and lower blood pressure. Sex and lifestyle were associated with both LDL-cholesterol and diastolic blood pressure, while age was associated with both systolic and diastolic blood pressure.

Previous studies examining medication adherence to secondary prevention of CHD or cardiovascular disease using pharmacy dispensing data have also found high adherence for LLDs with mean PDC of 0.76 [28] or 79.8% having PDC ≥0.80 [17]. Also adherence to antihypertensive drugs is found to be high with mean PDC of 0.77 [15]. The medication adherence found in the present study is even higher than what has been seen in these studies. There could be several explanations for this. First, we have only selected persistent prevalent medication users to enable calculation of PDC for the whole year before attendance in Tromsø 7. Most previous studies have included new users in the first months or years after treatment initiation or included a combination of new and prevalent users. The highest discontinuation rates have been found to appear in the first year after treatment initiation, and persistent users tend to have higher adherence than those who are nonpersistent [29]. Second, disease severity has been associated with higher adherence, and thus we anticipate higher adherence to secondary prevention of CHD compared with primary prevention [28]. Third, NorPD covers all dispensed medications in these medication groups, irrespective of reimbursement, and none of these medications are available over-the-counter in Norway. This

enables us to include all the medications that are actually available to the participants, which may not be the case in all other studies. Altogether, these patients seem to be highly adherent.

Despite the low nonadherence to LLDs in this patient group, it was significantly associated with a higher LDL-cholesterol. This agrees with other studies showing that adherence to LLDs is associated with reaching the recommended treatment goals for LDL-cholesterol [17, 18]. A Norwegian study by Munkhaugen et al also found that self-reported medication adherence to statins was associated with both lower LDL-cholesterol and achievement of the treatment goal for LDL-cholesterol [30]. Lowering LDL-cholesterol reduces the risk of a new coronary event [5]. In a previous study, we showed that only 9% of these participants reached the treatment goal of <1.8 mmol/L (<70 mg/dL) [11], which is surprising seen in the light of the high adherence shown in the current study. Even if more focus on the importance of adherence could lead to an increase in treatment goal achievement in this patient population, other actions such as increasing the prescribed daily dose of statins or adding ezetimibe, might also be necessary. In the current study we were not able to identify how much the LDL-cholesterol had been reduced from baseline, or whether dose increase could be justified. Previous studies have shown a larger LDL-cholesterol reduction with more intense statin treatment [5, 31, 32], and a more intense treatment seems to be necessary in our population. However, it is important to keep in mind that higher dosages of statins are more prone to give side-effects, which again might negatively affect the participants' adherence. Nocebo effects with statin treatment are also increasingly being recognized, further augmenting the risk of poor adherence and discontinuation of treatment [33, 34].

Neither systolic nor diastolic blood pressure were significantly affected by adherence to antihypertensive drugs in our analyses. This contrasts with other studies, where being adherent was associated with achieving blood pressure goals [15, 16, 19]. However, a Norwegian study by Sverre et al also found no association between adherence to

antihypertensive drugs, based on self-report, and blood pressure control [35]. In the same study, increased blood pressure was found to be associated with older age and higher BMI. We have previously found that 42% of our study population did not reach the recommended blood pressure goal (140/90 mmHg or 140/80 mmHg if they also had diabetes) and that self-reported use of antihypertensive drugs was not associated with achieving the treatment goal [11]. When we now have identified such a high adherence to these drugs among the persistent prevalent medication users in the same population, but no association with their blood pressure, a potential explanation could be that treatment intensity is too low. Our results also show the very clear association between higher age and higher blood pressure, which could be caused by arterial stiffening which increases with age and is associated with higher blood pressure [36]. It is also possible that elderly persons are not treated as intensely with antihypertensive drugs as those who are younger, which might be clinically sound. This has also been taken into account by the more recent European clinical guidelines from 2016 [8], contrary to the guidelines from 2012 [7] applied in this study. For patients over 60 years with a baseline systolic blood pressure over ≥160 mmHg, the new recommended systolic blood pressure goal is 140-150 mmHg. Treating hypertension in the oldest patients can be challenging, as they are usually more frail and more sensitive to potentially harmful side-effects such as reduced kidney function and orthostatic hypotension, which could lead to falls. Although reducing blood pressure is very important in CHD patients, it might not be possible, or even appropriate, to bring all patients down to the recommended blood pressure goal.

Though we have not assessed initiation and persistence in this study, Fig. 1 shows that about 12% of the participants had no prescriptions dispensed for each of these medication groups throughout the whole follow-up window from 2004 until they attended Tromsø 7, indicating they either never had such medications prescribed, or that they never initiated treatment. Of those who had been dispensed prescriptions for either of the medication groups, 15%

discontinued antihypertensive treatment or LLDs and 13% discontinued ASA before attending Tromsø 7. The proportion discontinuing treatment is lower than what has been found in previous Nordic studies [29, 37, 38], indicating that our study population does have good persistence. However, those who discontinue or do not initiate treatment might have an even higher risk of new coronary events. It should be further investigated how to identify these patient groups and assessed whether a closer treatment follow-up is warranted.

Strengths and limitations

A strength of this study was the use of two reliable data sources; the Tromsø Study, a reliable population-based data source with high attendance rate, where measurements of blood pressure and cholesterol were performed by trained personnel using standardized procedures and instruments, and NorPD, which includes information about all dispensings from Norwegian pharmacies. Using a follow-up window from 2004, when NorPD was established, enabled us to capture as many days covered with medication supplies as possible in the observation window, and hence estimate how much medication the participants had available during the observation window. Furthermore, the medications studied herein are prescription-only medications, we should therefore have captured all medications available to the participants. However, as we did not have any information about potential hospital stays, and medications dispensed to patients in hospitals are not included in NorPD, this could potentially lead to a slight underestimation of PDC.

One limitation is that we did not have information about prescribed daily dose as this is not available in NorPD. We therefore assumed a daily dose of one dosage unit. As most medications used for secondary prevention of coronary heart disease are taken once daily this is a fair assumption, though some medications, particularly some antihypertensives, might have a higher daily dosage (units per day), and this would lead us to overestimate the PDC. However, a validation of the self-reported use of these medications in this population, showed

that a daily dose of one dosage unit a day was a more accurate assumption than one defined daily dose (DDD) a day, which would have been the alternative [26].

As in other studies evaluating refill adherence, we cannot determine that having had the medications dispensed actually means that they have been consumed by the participants. We can however be quite certain that these medications are considered in use by the participants, as previously shown in the validation study [26].

Finally, and perhaps most importantly, the proportions of variance in LDL-cholesterol, and in systolic and diastolic blood pressure, explained by our models were low (4.2-9.9%), indicating that other factors also contribute to the observed variance. As this is an observational study, our results might also have been influenced by unmeasured confounders.

Conclusion

Adherence to lipid-lowering drugs, antihypertensive drugs and acetylsalicylic acid among persons with coronary heart disease was high despite low achievement of treatment goals for blood pressure and LDL-cholesterol. Adherence to lipid-lowering drugs was significantly associated with lower LDL-cholesterol, while adherence to antihypertensive drugs was not significantly associated with either systolic or diastolic blood pressure. This suggests that these participants might not receive optimal medication treatment, and that perhaps dosages, or number or combinations of medications are insufficient. More research is needed to explore this.

Declarations

Funding: No funding was received for conducting this study.

Conflicts of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material: The data that support the findings of this study are available from the Tromsø Study and the Norwegian Institute of Public Health, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Tromsø Study, the Norwegian Institute of Public Health and the Regional Committees for Medical and Health Research Ethics.

Authors' contributions: EP, RP, KHH, AEE, BHG, HS and MW contributed to the conception and/or design of the work. EP, AEE and HS contributed to the acquisition of data for the work. EP and RP conducted the analyses. EP drafted the manuscript. All contributed to the interpretation of data and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Regional Committee for Medical and Health Research Ethics of North Norway (2015/1775) and had an approved Data Protection Impact Assessment (DPIA) from UiT The Arctic University of Norway.

Consent to participate: All participants in the Tromsø Study have given written informed consent for their data to be used in research.

Consent for publication: Not applicable

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Figure legends

Fig. 1 Flowchart of medication users

Fig. 2 Defining proportion of days covered for prevalent medication users

Treatment period durations were defined by the number of medication units (e.g. tablets) dispensed at each treatment fill (dots). PDC was calculated for prevalent users based on treatment durations during the observation window (green). The mid panel shows one participant with 50 % adherence and one with perfect adherence according to PDC. Incident users (top) and nonpersistent users (bottom) were excluded

Abbreviations: PDC, proportion of days covered

Fig. 3 Distributions of proportion of days covered

Abbreviations: PDC, proportion of days covered

Tables

Table 1: Characteristics of the study population and the different subgroups

	Study population n = 1483		**Users of lipid-lowering drugs n = 1003**		**Users of antihypertensive drugs n = 1046**		**Users of acetylsalicylic acid n = 1042**	
Age (years), mean (sd)	68.7	(10.8)	69.5	(9.6)	70.7	(9.8)	69.7	(9.7)
Sex, n (%)								
Male	1037	(69.9)	730	(72.8)	730	(69.8)	765	(73.4)
BMI (kg/m^2), mean (sd)	28.4	(4.5)	28.4	(4.3)	28.7	(4.5)	28.4	(4.3)
Diabetes, n (%)								
Current	204	(11.1)	160	(16.0)	172	(16.4)	158	(15.2)
Previous	21	(1.4)	14	(1.4)	15	(1.4)	11	(1.1)
LDL-cholesterol (mmol/L), mean (sd)	2.9	(1.0)	2.6	(0.8)	2.7	(0.9)	2.7	(0.9)
Systolic blood pressure (mmHg), mean (sd)	135.9	(20.9)	136.5	(20.7)	137.1	(21.1)	136.6	(20.4)
Diastolic blood pressure (mmHg), mean (sd)	74.4	(9.9)	74.3	(9.7)	73.8	(9.7)	74.2	(9.8)

Abbreviations: BMI, body mass index; LDL, low-density-lipoprotein; sd, standard deviation

Table 2: Adherence to antihypertensive drugs, lipid-lowering drugs, acetylsalicylic acid and subgroups

	PDC, mean (sd)		**Proportion of participants with PDC ≥0.80, n (%)**	
Antihypertensive drugs (n = 1046)	0.94	(0.10)	963	(92.1)
ACE-inhibitor (n = 215)	0.98	(0.07)	208	(96.7)
ARB (n = 371)	0.96	(0.10)	348	(93.8)
Beta-blocker (n = 759)	0.96	(0.10)	708	(93.3)
CCB (n = 269)	0.97	(0.08)	259	(96.3)
Thiazide (n = 229)	0.95	(0.12)	205	(89.5)
Lipid-lowering drugs (n = 1003)	0.94	(0.12)	884	(88.1)
Statin (n = 987)	0.94	(0.12)	869	(88.0)
Acetylsalicylic acid (n = 1042)	0.97	(0.08)	992	(95.2)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; PDC, proportion of days covered; sd, standard deviation

Table 3: Multivariable linear regression models (i, iii and iii) showing factors associated with systolic and diastolic blood pressure and LDL-cholesterol.

	Systolic blood pressure (i)				**Diastolic blood pressure (ii)**				**LDL-cholesterol (iii)**			
Predictors	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*B*	*p*
Constant	87.990	8.300	0.000	<.001	81.698	3.882	0.000	<.001	2.807	0.303	0.000	<.001
Non-adherence antihypertensive drugs[1]	1.647	1.484	0.035	.267	0.876	0.694	0.040	.207				
Non-adherence lipid-lowering drugs[2]									0.190	0.050	0.124	**<.001**
Age	0.683	0.077	0.314	**<.001**	-0.141	0.036	-0.141	**<.001**	0.001	0.003	0.014	.714
Sex, male	-2.282	1.551	-0.048	.142	1.901	0.726	0.088	**.009**	-0.203	0.061	-0.115	**<.001**
Lifestyle 1[3]	-4.471	8.481	-0.019	.598	10.600	3.967	0.099	**.008**	1.174	0.322	0.138	**<.001**
Lifestyle 2[3]	-7.705	8.580	-0.028	.369	-2.277	4.013	-0.018	.571	-0.209	0.328	-0.021	.523
BMI	0.208	0.155	0.043	.180	0.098	0.072	0.045	.175	0.008	0.006	0.044	.191
Diabetes, current	-0.785	1.837	-0.014	.669	-1.027	0.859	-0.038	.232	-0.189	0.072	-0.087	**.009**
Diabetes, previous	-2.246	5.445	-0.013	.680	0.089	2.547	0.001	.972	-0.017	0.212	-0.003	.934
Observations	939				939				909			
R^2 / R^2 adjusted	0.107 / 0.099				0.071 / 0.063				0.050 / 0.042			

[1]1.1-log(PDC antihypertensive drugs)
[2]1.1-log(PDC lipid-lowering drugs)
[3]Lifestyle variables constructed using multidimensional scaling including self-reported smoking, alcohol use, diet and physical activity. Higher values of lifestyle 1 indicate an unhealthier lifestyle with more consumption of alcohol and red meat as well as more current smokers. Higher values of lifestyle 2 indicate more frequent consumption of omega 3.
Abbreviations: B, unstandardized beta; *β,* standardized beta; BMI, body mass index; LDL, low-density-lipoprotein; PDC, proportion of days covered; SE, standard error

Figure 1

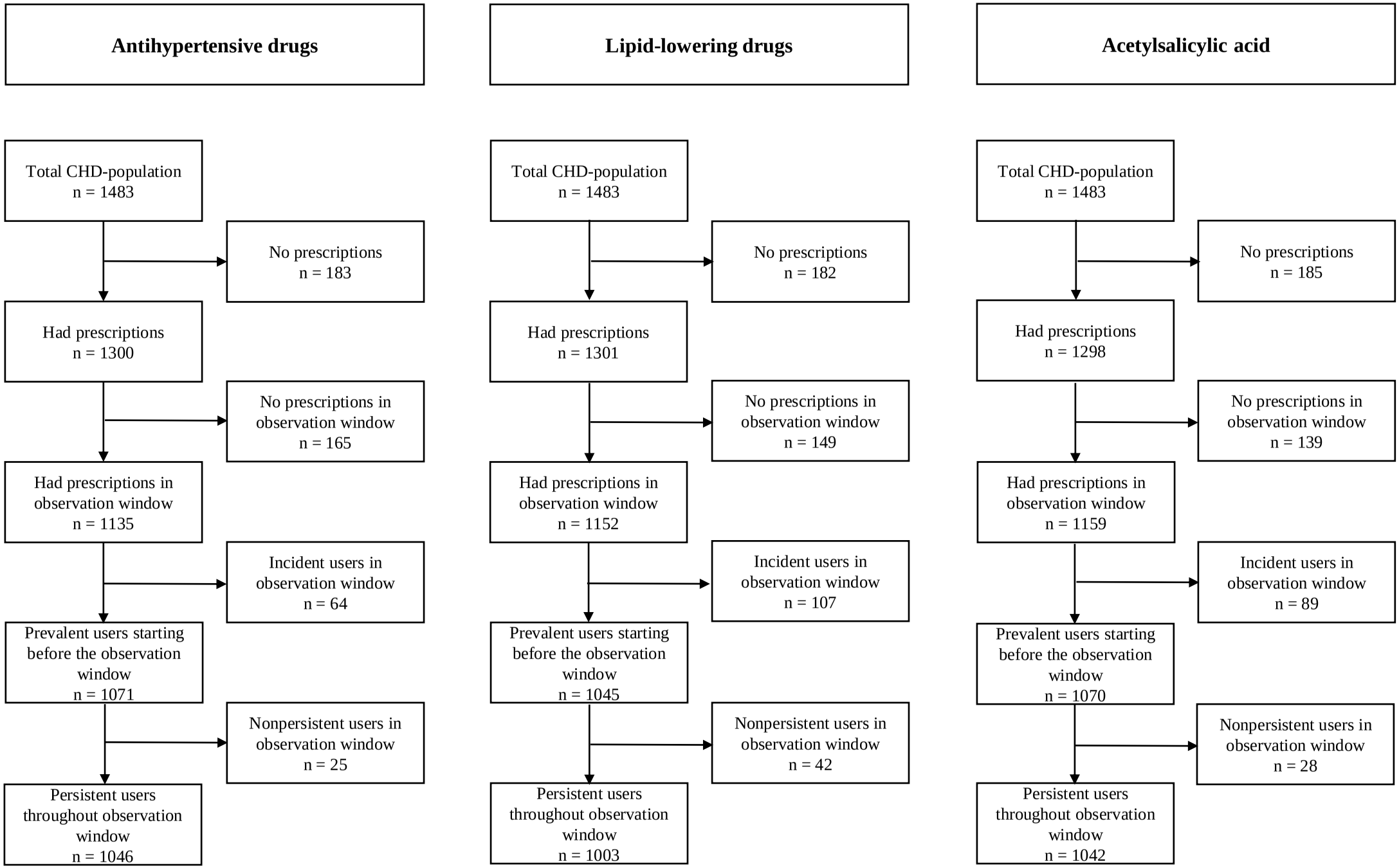

Antihypertensive drugs
Total CHD-population n = 1483
No prescriptions n = 183
Had prescriptions n = 1300
No prescriptions in observation window n = 165
Had prescriptions in observation window n = 1135
Incident users in observation window n = 64
Prevalent users starting before the observation window n = 1071
Nonpersistent users in observation window n = 25
Persistent users throughout observation window n = 1046
Lipid-lowering drugs
Total CHD-population n = 1483
No prescriptions n = 182
Had prescriptions n = 1301
No prescriptions in observation window n = 149
Had prescriptions in observation window n = 1152
Incident users in observation window n = 107
Prevalent users starting before the observation window n = 1045
Nonpersistent users in observation window n = 42
Persistent users throughout observation window n = 1003
Acetylsalicylic acid
Total CHD-population n = 1483
No prescriptions n = 185
Had prescriptions n = 1298
No prescriptions in observation window n = 139
Had prescriptions in observation window n = 1159
Incident users in observation window n = 89
Prevalent users starting before the observation window n = 1070
Nonpersistent users in observation window n = 28
Persistent users throughout observation window n = 1042

Figure 2

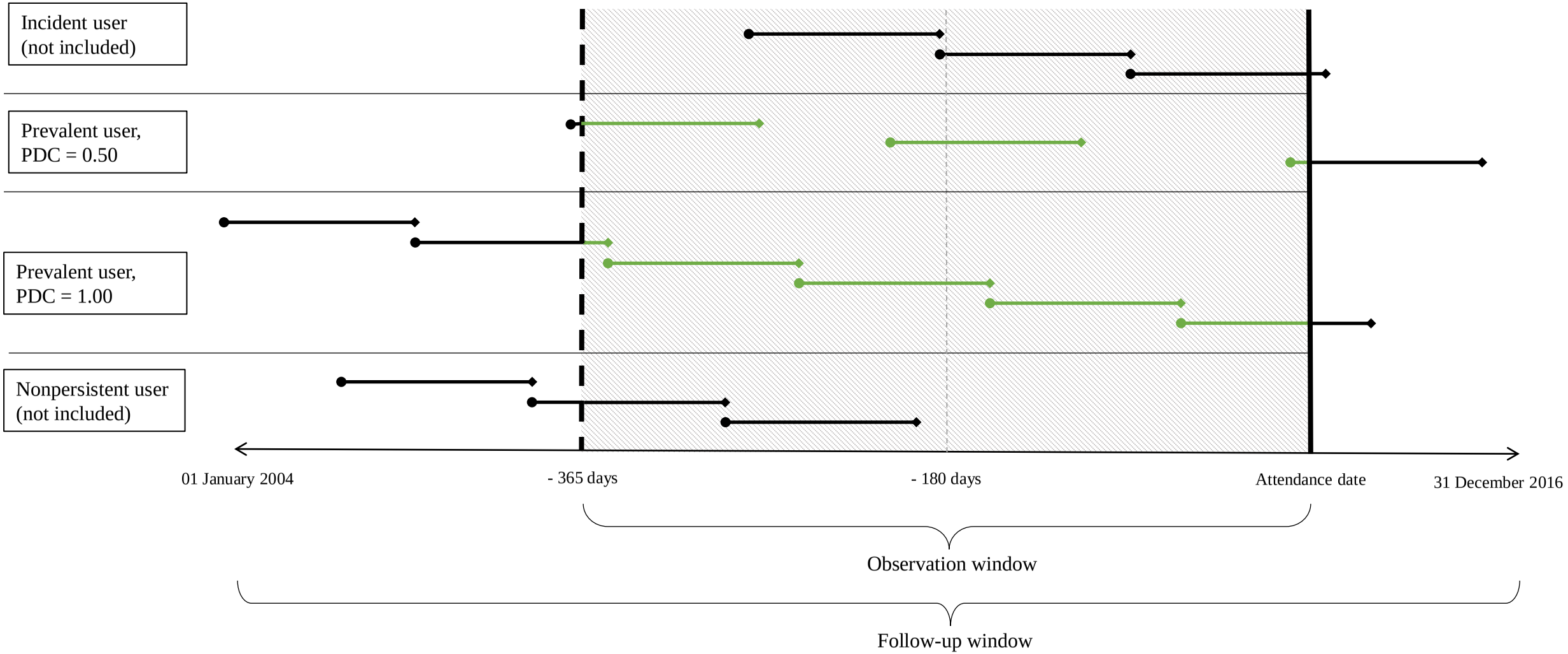
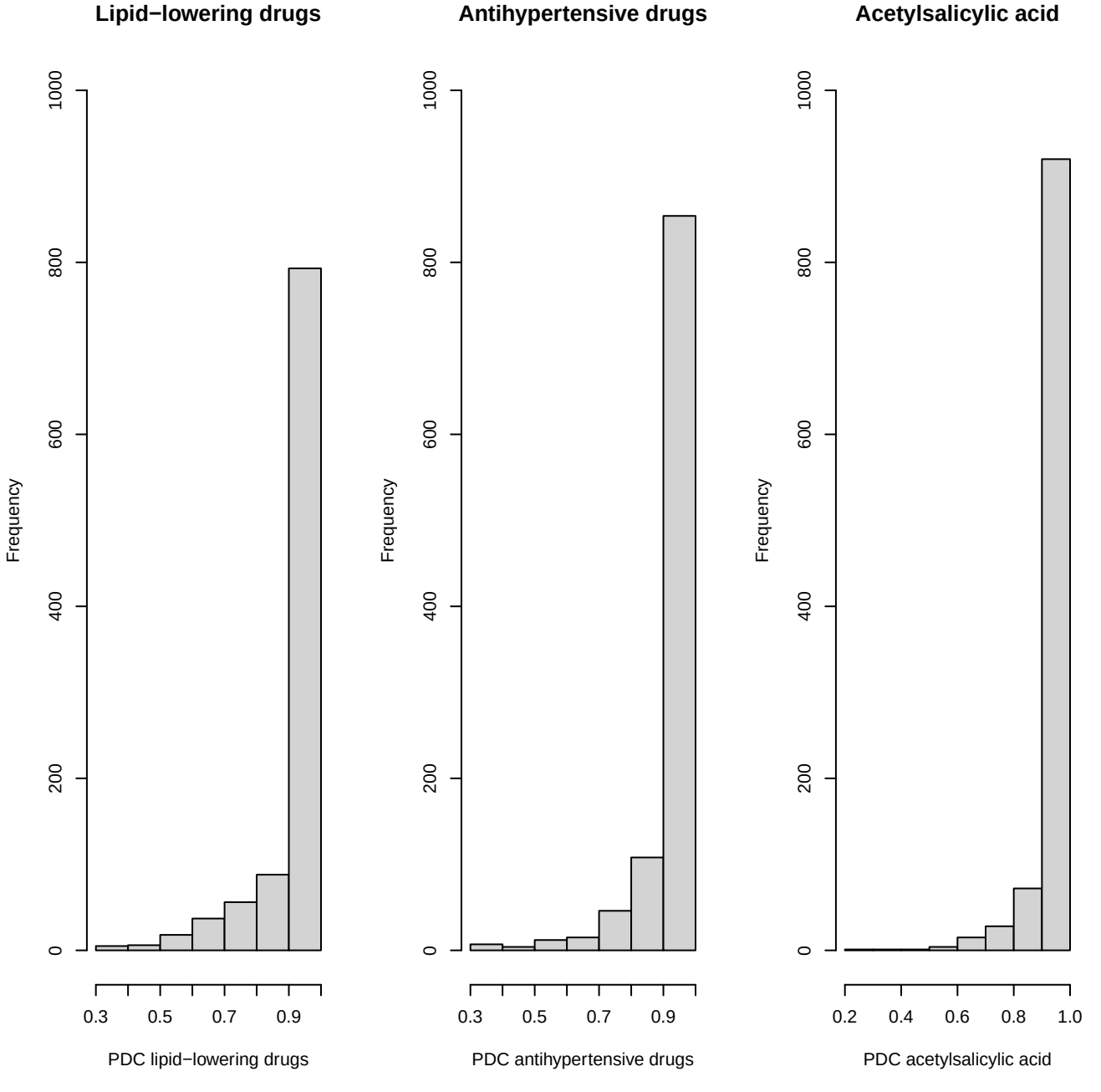

Incident user
(not included)
Prevalent user,
PDC = 0.50
Prevalent user,
PDC = 1.00
Nonpersistent user
(not included)
01 January 2004
- 365 days
- 180 days
Attendance date
31 December 2016
Observation window
Follow-up window

Figure 3


Lipid−lowering drugs
Antihypertensive drugs
Acetylsalicylic acid
Frequency
0
200
400
600
800
1000
0.3
0.5
0.7
0.9
0.2
0.4
0.6
0.8
1.0
PDC lipid−lowering drugs
PDC antihypertensive drugs
PDC acetylsalicylic acid

Supplementary material

Medication adherence among persons with coronary heart disease and associations with blood pressure and low-density-lipoprotein-cholesterol

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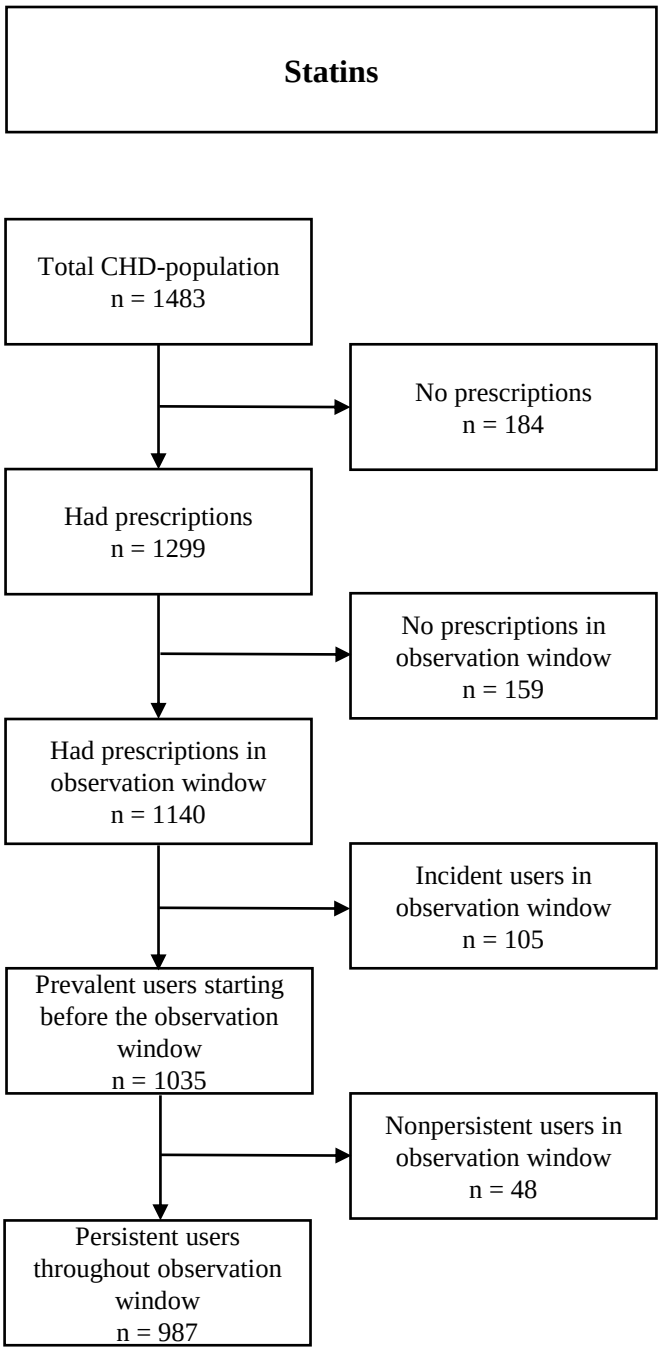
Content:

Supplementary table 1: Overview of ATC-codes included in the three medication categories

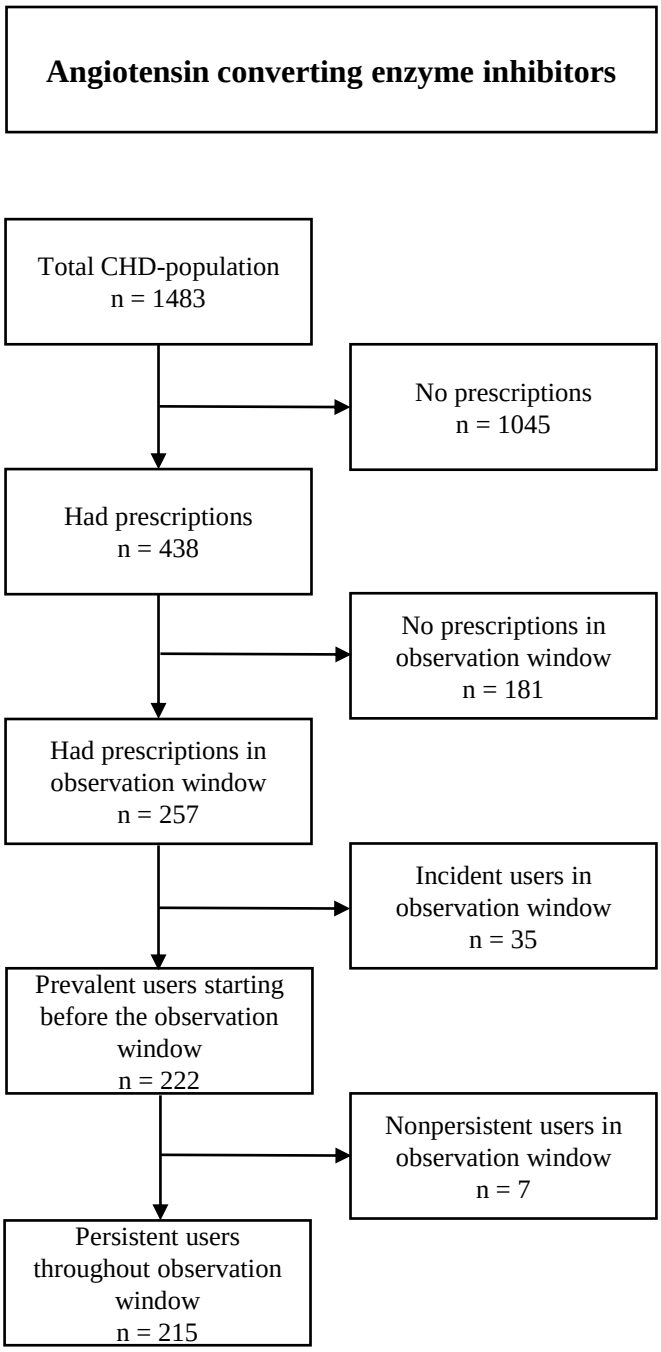
Medication	ATC-codes
Acetylsalicylic acid	
Acetylsalicylic acid	B01AC06
Lipid lowering drugs	
Statins	C10AA, C10BA
Other lipid lowering drugs	C10AC, C10AX, C10
Antihypertensive drugs	
ACE inhibitors	C09A, C09B
ARBs	C09C, C09D
Beta-blockers	C07
CCBs	C08, C09BB, C09DB, C09DX01, C09DX03
Thiazides	C03A, C03EA, C07B, C09BA, C09DA, C09DX01, C09DX03
Other antihypertensives	C02, C03C, C03D, C03EA, C03X

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ATC, anatomical therapeutic chemical; CCB, calcium channel blocker

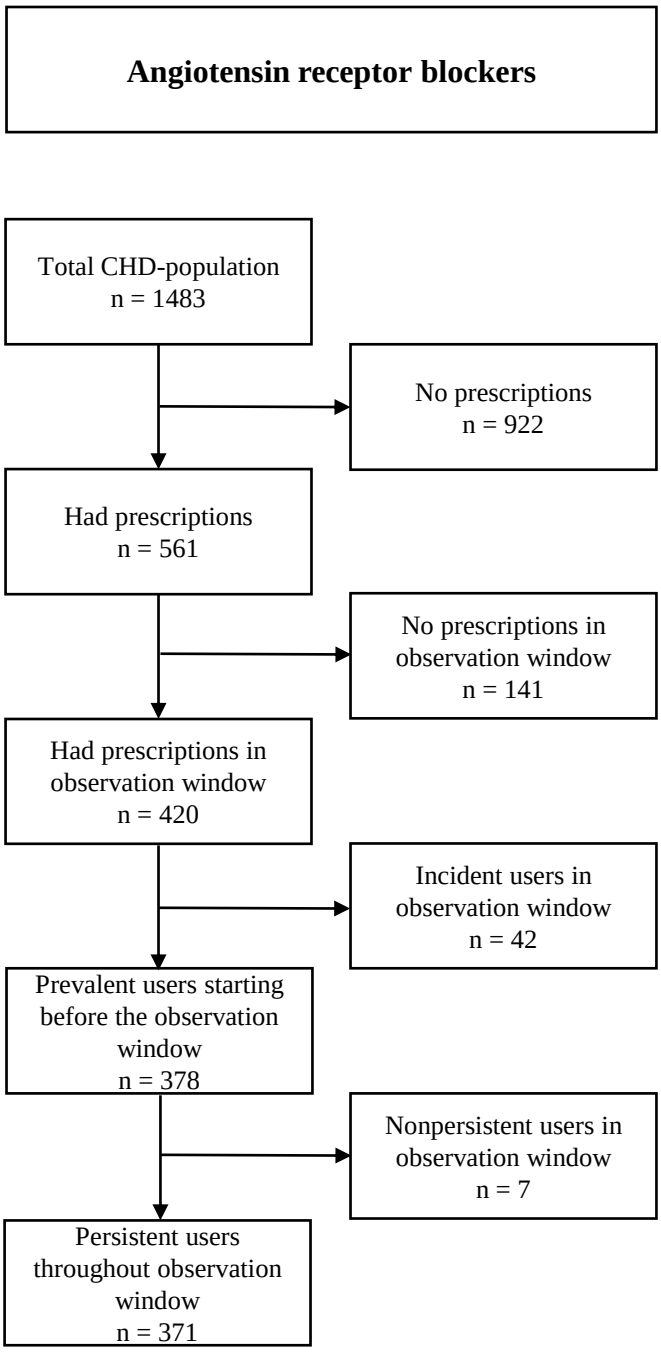
Online resouce 2



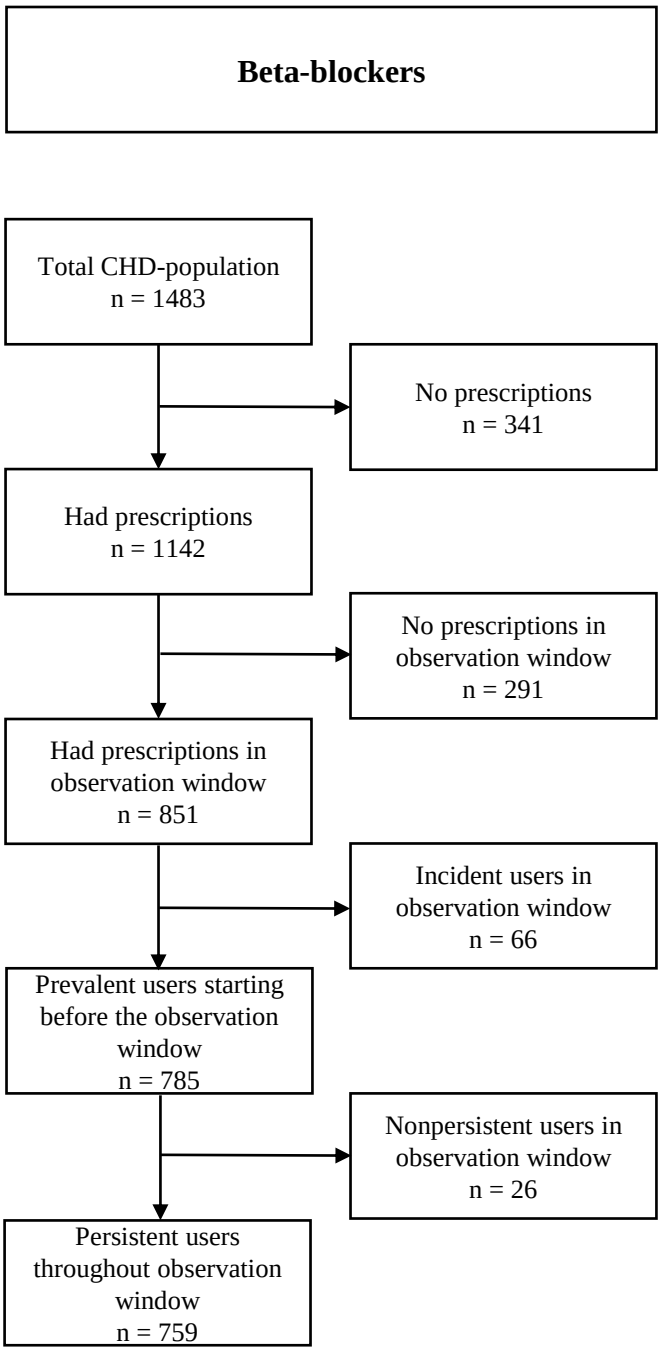
Online resouce 2



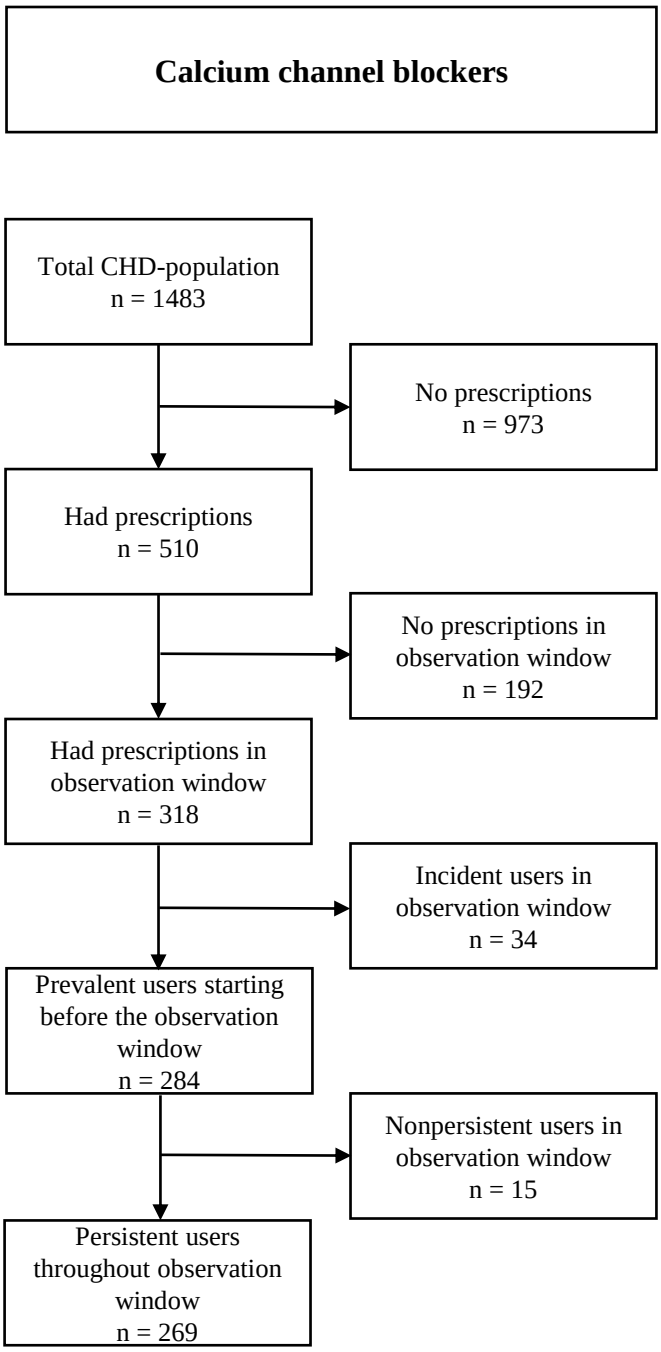
Online resouce 2



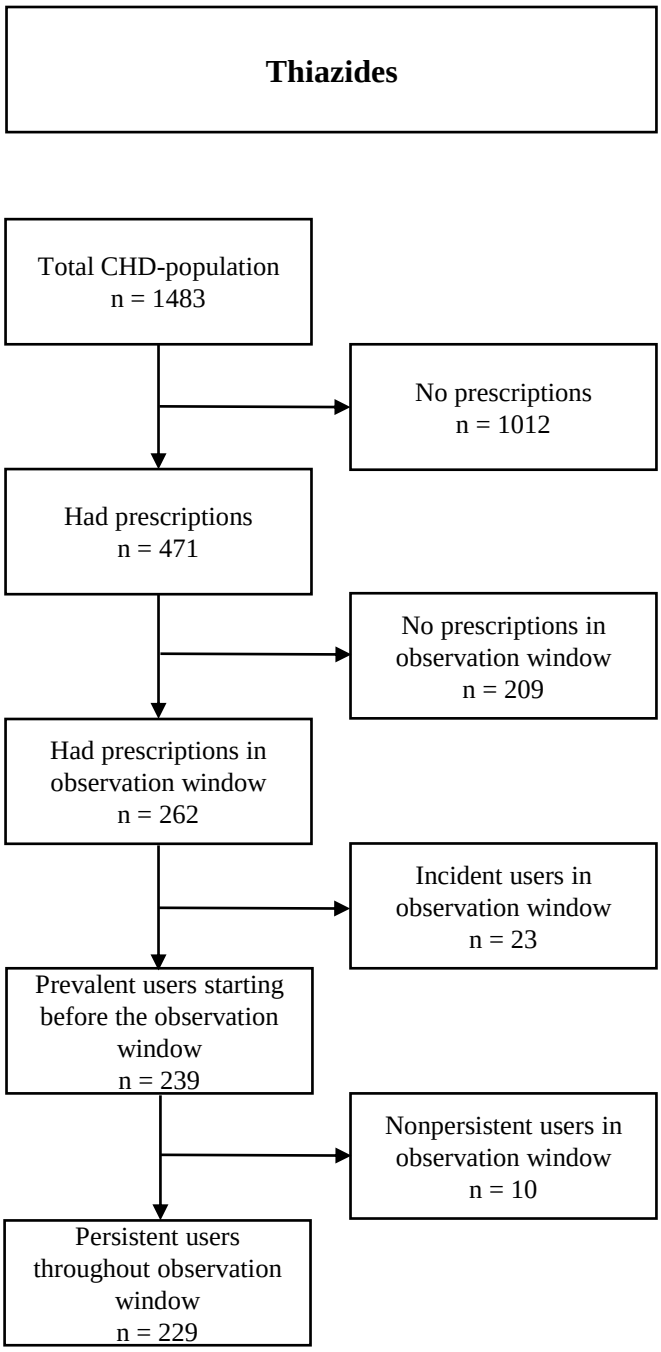
Online resource 2



Online resource 2



Online resouce 2



Supplementary 3: Lifestyle variables

Explanation for making and interpreting the lifestyle variables:

We constructed two variables containing a gradient of lifestyle including ordinal variables on alcohol consumption, smoking, diet and physical activity (see table below).

The variables were made in R using the package "vegan" (see R code below). First the dissimilarity in the original variables were calculated using gower distance which is the preferred choice for heterogeneous variables. This distance matrix was then used to identify four clusters using hierarchical clustering. Next, multidimensional scaling was preformed on the distance matrix made earlier, giving the sets of points with distances equaling the dissimilarities in the different variables used (alcohol consumption, smoking, diet and physical activity, see table below). The points from the multidimensional scaling were saved as the two lifestyle variables used in further analyses.

The points from the multidimensional scaling with colors indicating the clusters identified are shown in the figure below. To show the correlation with age, red isolines of age is added onto the plot. To see which of the original variables contribute to the dissimilarities in lifestyle we conducted a correspondence analysis as shown in the second plot in the figure. This shows that lifestyle variable 1 is influenced by especially alcohol consumption, but also consumption of read meat and smoking, so the participants represented by the blue and red colored clusters have a higher consumption of alcohol and red meat and are more likely to be smokers, while the opposite is shown for those in the green and orange clusters. Lifestyle variable 2 appears to be more influenced by intake of cod liver oil or omega 3, where those in the green and orange clusters more often take cod liver oil or omega 3.

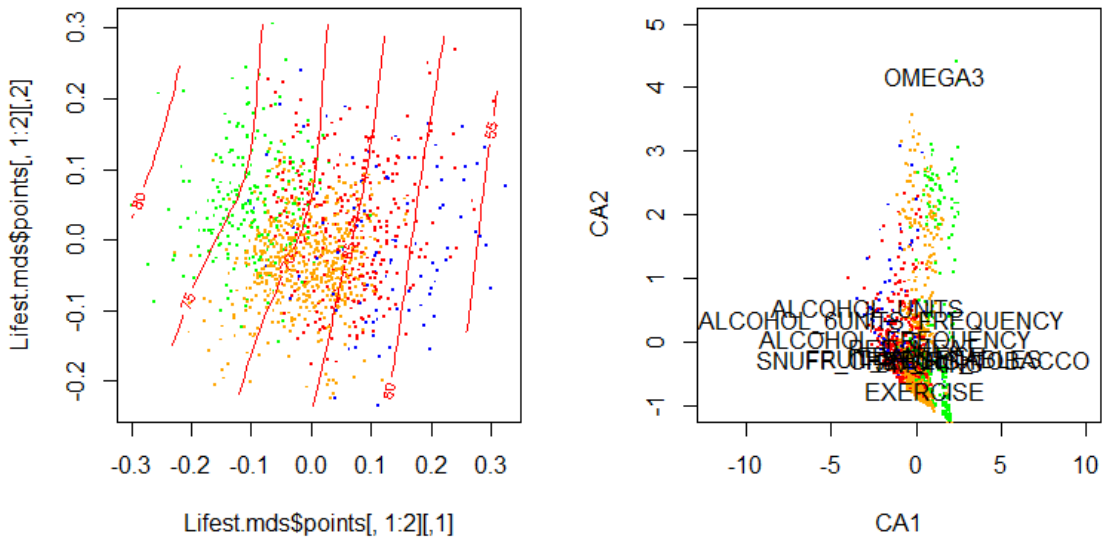


Figure: Plots of the first two dimensions of the multidimensional scaling analyses (left) and the correspondence analysis (right), both with colors indicating the clusters identified

Online resource 3

Table: Distribution participants' answer to variables included in new latent lifestyle variables

	Study population n = 1483		Users of lipid-lowering drugs n = 1003		Users of antihypertensive drugs n = 1046		Users of acetylsalicylic acid n = 1042	
	n	(%)	n	(%)	n	(%)	n	(%)
Alcohol frequency								
Never	157	(10.6)	110	(11.0)	124	(11.9)	111	(10.7)
Monthly or less frequently	297	(20.0)	184	(18.3)	216	(20.7)	198	(19.0)
2-4 times a month	593	(40.0)	409	(40.8)	396	(37.9)	424	(40.7)
2-3 times a week	313	(21.1)	214	(21.3)	220	(21.0)	221	(21.2)
4 or more times a week	122	(8.2)	85	(8.5)	89	(8.5)	87	(8.3)
Alcohol units usually drunk when drinking alcohol								
0	157	(10.6)	109	(10.9)	125	(12.0)	110	(10.6)
1-2	717	(48.4)	481	(48.0)	520	(49.7)	499	(47.9)
3-4	472	(31.8)	323	(32.2)	309	(29.5)	339	(32.5)
5 or more	131	(8.8)	86	(8.6)	86	(8.2)	89	(8.5)
Alcohol more than 6 units frequency								
Never	852	(57.5)	585	(58.3)	643	(61.5)	606	(58.2)
Less frequently than monthly	478	(32.2)	313	(31.2)	296	(28.3)	334	(32.1)
Monthly	101	(6.8)	68	(6.8)	69	(6.6)	69	(6.6)
Weekly	27	(1.8)	18	(1.8)	17	(1.6)	15	(1.4)
Daily or almost daily	5	(0.3)	3	(0.3)	5	(0.5)	4	(0.4)
Smoking								
Now, daily	196	(13.2)	122	(12.2)	124	(11.9)	135	(13.0)
Now, sometimes	31	(2.1)	19	(1.9)	19	(1.8)	19	(1.8)
Previously	883	(59.5)	639	(63.7)	645	(61.7)	650	(62.4)
Never	373	(25.2)	223	(22.2)	258	(24.7)	238	(22.8)
Snuff or chewing tobacco								
Now, daily	91	(6.1)	62	(6.2)	61	(5.8)	63	(6.0)

Now, sometimes	2	(0.1)	2	(0.2)	2	(0.2)	2	(0.2)
Previously	76	(5.1)	45	(4.5)	40	(3.8)	50	(4.8)
Never	1311	(88.4)	892	(88.9)	940	(89.9)	924	(88.7)
Red meat								
0-1 times per month	88	(5.9)	57	(5.7)	58	(5.5)	61	(5.9)
2-3 times per month	322	(21.7)	224	(22.3)	222	(21.2)	221	(21.2)
1-3 times per week	926	(62.4)	621	(61.9)	667	(63.8)	663	(63.6)
4-6 times per week	91	(6.1)	59	(5.9)	53	(5.1)	58	(5.6)
Once a day or more	14	(0.9)	10	(1.0)	7	(0.7)	10	(1.0)
Fruits/vegetable/berries								
0-1 times per month	15	(1.0)	11	(1.1)	11	(1.1)	12	(1.2)
2-3 times per month	56	(3.8)	33	(3.3)	37	(3.5)	38	(3.6)
1-3 times per week	314	(21.2)	221	(22.0)	215	(20.6)	227	(21.8)
4-6 times per week	413	(27.9)	282	(28.1)	295	(28.2)	286	(27.4)
Once a day or more	654	(44.1)	432	(43.1)	461	(44.1)	458	(44.0)
Lean fish								
0-1 times per month	49	(3.3)	25	(2.5)	22	(2.1)	22	(2.1)
2-3 times per month	201	(13.6)	134	(13.4)	124	(11.9)	134	(12.9)
1-3 times per week	1020	(68.8)	703	(70.1)	738	(70.6)	740	(71.0)
4-6 times per week	167	(11.3)	109	(10.9)	125	(12.0)	119	(11.4)
Once a day or more	14	(0.9)	11	(1.1)	10	(1.0)	8	(0.8)
Fat fish								
0-1 times per month	163	(11.0)	103	(10.3)	114	(10.9)	101	(9.7)
2-3 times per month	502	(33.9)	340	(33.9)	351	(33.6)	356	(34.2)
1-3 times per week	696	(46.9)	477	(47.6)	494	(47.2)	501	(48.1)
4-6 times per week	64	(4.3)	42	(4.2)	48	(4.6)	46	(4.4)
Once a day or more	21	(1.4)	15	(1.5)	11	(1.1)	15	(1.4)
Omega 3 or cod liver oil								
Never	1067	(71.9)	717	(71.5)	758	(72.5)	740	(71.0)
Sometimes	184	(12.4)	123	(12.3)	131	(12.5)	136	(13.1)
Daily during the winter season	57	(3.8)	34	(3.4)	33	(3.2)	36	(3.5)

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Daily	137	(9.2)	103	(10.3)	97	(9.3)	107	(10.3)
Exercise frequency								
Never	143	(9.6)	88	(8.8)	114	(10.9)	98	(9.4)
Less than once a week	194	(13.1)	126	(12.6)	138	(13.2)	128	(12.3)
Once a week	202	(13.6)	141	(14.1)	153	(14.6)	145	(13.9)
2-3 times a week	541	(36.5)	372	(37.1)	366	(35.0)	381	(36.6)
Approximately every day	369	(24.9)	255	(25.4)	253	(24.2)	269	(25.8)

R-code:

```
#Loading relevant libraries
library(foreign)
library(mgcv)
library(vegan)

#Including relevant variables
Lifest<-pred_ext[,c(7, 31:36, 38:41, 43)]
colnames(Lifest) <- c('AGE', 'ALCOHOL_FREQUENCY', 'ALCOHOL_UNITS',
'ALCOHOL_6UNITS_FREQUENCY', 'SMOKING', 'SNUFF_CHEWING_TOBACCO',
'OMEGA3', 'RED_MEAT', 'FRUIT_VEGETABLES', 'LEAN_FISH', 'FAT_FISH',
'EXERCISE')

#Making Gower distance matrix and defining clusters
Lifest.D<-vegdist(na.omit(Lifest[,-1]),method="gower")
Lifest.hclust<-hclust(Lifest.D)
plot(Lifest.hclust)
Lifecl4<-cutree(Lifest.hclust,4)


#Making and plotting results from multidimensional scaling
par(mfrow=c(1,2))
Lifest.mds<-cmdscale(Lifest.D, eig=T)
plot(Lifest.mds$points[,1:2],type="n")
points(Lifest.mds$points[,1:2],pch=".",cex=2,col=c("red","orange","green","blue")[Lifecl4])
ages<-Lifest[as.numeric(rownames(na.omit(Lifest[,-1]))),1]
ordisurf(Lifest.mds,ages,add=T)

#Running and plotting correspondence analysis to determine which variables contribute to the
#lifestyle variables
Lifest.ca<-cca(na.omit(Lifest[,-1]))
plot(Lifest.ca$CA$u,type="n", xlim = c(-5.5,10), ylim = c(-1,3))
points(Lifest.ca$CA$u,pch=".",cex=2,col=c("red","orange","green","blue")[Lifecl4])
text(Lifest.ca$CA$v,labels=rownames(Lifest.ca$CA$v))
```

Appendix 1

Information brochure Tromsø 7

UiT

NORGES
ARKTISKE
UNIVERSITET

Vil du være med i **Tromsøundersøkelsen?**

UNIVERSITETET I TROMSØ

Forespørsel om deltakelse i Tromsøundersøkelsen

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er en folkehelseundersøkelse. Formålet er å samle inn opplysninger til forskning som gir økt kunnskap om helse og sykdom, og hvordan folkehelsen kan forbedres gjennom forebygging og behandling.

Tromsøundersøkelsen startet i 1974 med bakgrunn i den høye forekomsten av hjerte -og karsykdom i Nord-Norge. Siden den gang er undersøkelsen gjennomført med 6-7 års mellomrom og dette er den sjuende runden.

Ved å delta bidrar du til viktig forskning om forekomst, forebygging og behandling av sykdom, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Ditt bidrag teller!

Hvorfor spør vi deg?

Alle innbyggere i Tromsø kommune fra 40 år og oppover spørres om å delta. I tillegg inviterer vi ca.1000 personer i alderen 21-25 år. Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk.

Sammen med denne informasjonsbrosjyren finner du en invitasjon med praktiske opplysninger om undersøkelsen.

Det er gratis å delta i Tromsøundersøkelsen. Trenger du videre undersøkelse eller oppfølging av fastlegen eller spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Alle deltakere inviteres til en hovedundersøkelse som omfatter spørreskjema, intervju, blodprøver og undersøkelser. Et helt tilfeldig utvalg av deltakere inviteres tilbake til en spesialundersøkelse som omfatter flere prøver og mer omfattende undersøkelser. Alle undersøkelsene gjennomføres av helsepersonell.

Tilbakemelding

Noen uker etter undersøkelsen får du et brev med noen resultater, det vil si høyde, vekt, BMI, hemoglobin, blodtrykk, kolesterolnivå og om du har diabetes. Det gis ikke rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger. Dersom prøveresultatet viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du få råd om det. Ved behov for henvisning til spesialist, sørger vi for å sende henvisning.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat krever rask legebehandling, vil du likevel bli kontaktet.

Du vil også få informasjon om undersøkelsen underveis gjennom aviser, sosiale medier (Facebook, Twitter m.m) samt på arrangementer som "Lørdagsuniversitetet" og "Forskningsdagene".

Frivillig deltakelse

Det er frivillig å delta i Tromsøundersøkelsen.
Om du sier ja til å delta, kan du når som helst trekke tilbake samtykket.

Hva omfatter den sjuende Tromsøundersøkelsen?

Hva skal vi forske på?

I denne runden av Tromsøundersøkelsen er det mer enn 50 prosjekter som skal forske på forekomst, forebygging og behandling av folkehelseproblemer.

Det skal blant annet forskes på hjerte- og karsykdommer, kreft, lunge-sykdommer, aldring og demens, fedme, diabetes, legemiddelbruk, psykisk helse, kronisk smerte, tannhelse, muskel- og skjelettplager, risikofaktorer som alkohol, fysisk aktivitet og kosthold, nyrer og urinveier, hudproblemer, miljøgifter, infeksjoner og antibiotikaresistens, nervesystemet, sosial ulikhet, samspill mellom arv og miljø, søvn og bruk av helsetjenester.

Du finner mer informasjon om forskningen på vår internettside, www.tromsoundersokelsen.no

Spørreskjema

Deltakernes informasjon om egen helse er en svært viktig del av Tromsø-undersøkelsen. Vi ber deg derfor fylle ut to spørreskjema. Alle spørsmål kan besvares på nett. Det ene skjemaet er vedlagt i papirform, hvis du foretrekker det. Fyll det gjerne ut før du møter opp så sparer du tid under undersøkelsen. Hvis du trenger assistanse vil personalet hjelpe deg på undersøkelsen hvor det også er satt opp egne datamaskiner til dette.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og kliniske undersøkelser.

Du kan delta på Tromsøundersøkelsen selv om du ikke ønsker å være med på alle deler av undersøkelsen.

Hovedundersøkelsen

Helsepersonell veileder deg gjennom undersøkelsen som varer ca. en time hvis du har fylt ut spørreskjemaene på forhånd. Du får også time til spesialundersøkelsen hvis du er valgt ut til denne.

Vi starter med noen enkle spørsmål knyttet til undersøkelsene du skal gjennomføre. Videre måler vi høyde, vekt, hofte- og livvidde, blodtrykk og puls.

Det tas deretter prøver og gjøres noen kliniske undersøkelser:

Blodprøve. Det tas blodprøver til bruk for forskning som samlet er mye mindre enn det en blodgiver gir. Det fryses ned prøver til bruk for senere analyser og forskning. Arvestoff (DNA/RNA) vil bli lagret til bruk for forskning.

Bakterieprøve fra nese og hals for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøvene tas med en fuktet vattpensel.

Spyttprøver til bruk for forskning knyttet til tannhelse, virusinfeksjon og kreft.

Smerteølsomhet måles med to metoder. Først holder du hånden i kaldt vann i opptil 90 sekunder,deretter får du en blodtrykksmansjett plassert rundt leggen som blåses opp. Underveis angir du hvor mye smerte du opplever, og kan avbryte testene når som helst hvis det blir for ubehagelig.

Tannsjekk som omfatter et røntgenbilde av kjeven, registrering av hull i tennene og betennelsessykdom i tannkjøttet.

Fysisk aktivitet og kosthold. Utvalgte deltakere blir bedt om å registrere fysisk aktivitet ved bruk av aktivitetsmåler og registrering av kosthold i en periode.

Du får også utdelt utstyr for innlevering av urin- og avføringsprøve hvis du er valgt ut til spesialundersøkelsen.

Spesialundersøkelsen

Et tilfeldig utvalg av deltakere inviteres til spesialundersøkelsen som gjennomføres noen uker etter hovedundersøkelsen. Denne varer totalt ca. 2 timer, avhengig av hvor mange deler du blir spurt om å være med på.

Ved oppmøte vil urinprøvene samles inn, og det tas noen nye blodprøver. Deler av blodprøvene fryses ned for senere forskning beskrevet i denne brosjyren.

Videre inviteres du til én eller flere av disse undersøkelsene:

EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen.

Kognitiv funksjon testes ved hjelp av enkle spørsmål knyttet til gjenkjenning av ord, kopling av symboler og tall samt grad av fingerbevegelighet.

Fysisk funksjon undersøkes ved å teste balanse, gange og gripestyrke.

Ultralyd av halspulsåre gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.

Fotografering av øyebunnen gir bilder som både sier noe om synet og om tilstanden til blodkarene i kroppen. Det gis en øyendråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og er borte etter en time. I tillegg gjøres det en enkel synstest som du får svar på umiddelbart.

Lungefunksjonen testes ved at du puster så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din. I tillegg vil det gjøres lydopptak av lungelyder og hjertelyder.

Måling av beintetthet. Ved hjelp av ultralyd foretas det beintetthetsmåling som brukes til å undersøke risiko for beinskjørhet og brudd.

Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.

Videre bruk av opplysninger og prøver i forskning

Personvern

All informasjon du gir til Tromsøundersøkelsen behandles med respekt for personvern og privatliv, og i samsvar med lover og forskrifter.
Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn skal bare brukes til godkjente forskningsformål. Det vil ikke være mulig å identifisere deg når resultatene av forskningen publiseres.

UiT Norges arktiske universitet ved universitetsdirektøren er ansvarlig for behandlingen av personopplysninger. Tromsøundersøkelsen har konsesjon fra Datatilsynet. Regional komité for medisinsk og helsefaglig forskningsetikk i Nord-Norge (REK nord) har gjort en etisk og helsefaglig vurdering av undersøkelsene som gjennomføres, samt godkjent innsamlingen av prøver.

Hvilke data lagres i Tromsøundersøkelsen?

I Tromsøundersøkelsen lagres opplysninger gitt av deltakere i de forskjellige rundene av Tromsøundersøkelsen. Det lagres også opplysninger om kreftdiagnoser og dødsårsaker fra Kreftregisteret og Dødsårsaksregisteret.
For deltakere som har eller får diagnoser innen hjerte- og karsykdom, diabetes og beinbrudd, innhentes opplysninger fra sykejournalen i spesialist- og primærhelsetjenesten som er nødvendig for å kvalitetssikre aktuelle diagnoser. Dette for å sikre forskning av høy kvalitet. Tilsvarende vil også kunne bli aktuelt for andre sykdommer det forskes på i Tromsøundersøkelsen.

Hvordan lagres dine opplysninger og prøver?

Alle opplysningene og prøvene lagres uten navn og fødselsnummer.

En kode knytter deg til dine opplysninger og prøver. Det er kun noen få autoriserte personer som kan finne tilbake til deg gjennom en egen kodenøkkel.

De biologiske prøvene lagres i godkjent forskningsbiobank ved Institutt for samfunnsmedisin, UiT. Leder av Tromsøundersøkelsen er ansvarlig for biobanken. Den er registrert i Folkehelseinstituttets Biobankregister (nr 2397). Det biologiske materialet kan bare brukes etter godkjenning fra REK.

Utlevering av opplysninger og prøver til forskere

Hvis du sier ja til å delta i studien, samtykker du til at dine opplysninger og prøver kan brukes videre i forskning på ubestemt tid. Medisinsk forskning forandrer seg hele tiden, og i fremtiden kan data bli brukt i forskningsprosjekter forutsatt at det er i samsvar med gjeldende lover og forskrifter.

Alle forskningsprosjekter som får data fra Tromsøundersøkelsen må være i samsvar med lover og forskrifter. Prosjektleder må tilhøre en kompetent forskningsinstitusjon. Den enkelte forsker vil kun få tilgang til personidentifiserende opplysninger etter å ha innhentet nødvendige godkjenninger fra REK, og/eller Datatilsynet.

I noen forskningsprosjekter kan prøver og avidentifiserte opplysninger bli utlevert til andre land. Det vil skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

I noen prosjekter kan det bli aktuelt å kontakte deg igjen for å samle inn flere data, f.eks. ved spørreskjema, intervju eller kliniske undersøkelser. Du vil da få ny informasjon og bes om nytt samtykke til det konkrete prosjektet.

Ved å delta i Tromsøundersøkelsen bidrar du til viktig forskning på sykdom og helse, oppbygging av fagmiljøer og bedre pasientbehandling.

Sammenstilling med andre registre

I noen forskningsprosjekter vil opplysninger om deg kunne bli sammenstilt med:

Opplysninger du har gitt i tidligere runder av Tromsøundersøkelsen hvis du har deltatt i Tromsøundersøkelsen før.

Opplysninger fra barn, søsken, foreldre og besteforeldre som har deltatt i Tromsøundersøkelsen.

Opplysninger om deg i nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregister, Kreftregisteret, Norsk pasientregister, Hjerte- og karregisteret, Dødsårsaksregisteret, infeksjonsregistre og andre nasjonale sykdoms- og kvalitetsregistre.

Helseopplysninger om deg fra primær- og spesialisthelsetjenesten.

Opplysninger om sosiale forhold som arbeid, utdanning, inntekt, boforhold osv. fra registre hos bl.a. Statistisk sentralbyrå og NAV.

Slike sammenstillinger krever som regel forhåndsgodkjenning av offentlige instanser, som REK og/eller Datatilsynet.

Rett til innsyn og sletting av dine opplysninger og prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller er brukt i vitenskapelige artikler.

Finansiering

Tromsøundersøkelsen er finansiert av UiT Norges arktiske universitet, Helse Nord RHF, Universitetssykehuset Nord-Norge (UNN) samt ulike forskningsfond.

Forsikring

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Samtykke til deltakelse i studien

Hvis du vil delta i den sjuende Tromsøundersøkelsen, må du gi skriftlig samtykke ved oppmøte. Personalet vil gi mer informasjon og svare deg dersom du har spørsmål i forbindelse med samtykket.

Du kan når som helst trekke tilbake samtykket ditt.

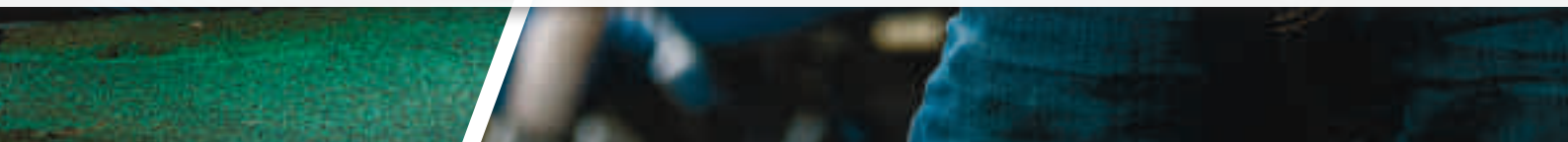
Her finner du oss:

Heiloveien 6 (tidligere Langnes legesenter)
9015 Tromsø

Telefon 77 62 07 00
Epost tromso7@uit.no
Nettside www.tromsoundersokelsen.no

Tromsø-undersøkelsen

UNIVERSITETET I TROMSØ



Appendix 2

Questionnaire 1 Tromsø 7

The Tromsø Study
2015–2016

CONFIDENTIAL

The questionnaire will be optically read. Please, use blue or black inked pen only. Use block lettering. Refrain from the use of comma.

Date for filling in the questionnaire: ☐☐☐☐☐☐

HEALTH AND DISEASES

1.1 How do you in general consider your health to be?

Excellent	Good	Neither good nor bad	Bad	Very bad
☐	☐	☐	☐	☐

1.2 How is your health now compared to others of your age?

Excellent	Good	Neither good nor bad	Bad	Very bad
☐	☐	☐	☐	☐

1.3 Have you ever had, or do you have?
Tick once for each line.

	No	Yes, currently	Previously, not now	Age first time
High blood pressure	☐	☐	☐	☐☐
Heart attack	☐		☐	☐☐
Heart failure	☐	☐	☐	☐☐
Atrial fibrillation	☐	☐	☐	☐☐
Angina pectoris *(heart cramp)*	☐	☐	☐	☐☐
Cerebral stroke / brain haemorrhage	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Kidney disease, not including urinary tract infection *(UTI)*	☐	☐	☐	☐☐
Bronchitis / emphysema / COPD	☐	☐	☐	☐☐
Asthma	☐	☐	☐	☐☐
Cancer	☐	☐	☐	☐☐
Rheumatoid Arthritis	☐	☐	☐	☐☐
Arthrosis	☐	☐	☐	☐☐
Migraine	☐	☐	☐	☐☐
Psychological problems for which you have sought help	☐	☐	☐	☐☐

1.4 Do you have persistent or constantly recurring pain that has lasted for three months or more?

☐ No ☐ Yes

DENTAL HEALTH

2.1 How do you consider your own dental health to be?

	1	2	3	4	5	
Very bad	☐	☐	☐	☐	☐	Excellent

2.2 How satisfied or dissatisfied are you with your teeth or denture?

	1	2	3	4	5	
Very dissatisfied	☐	☐	☐	☐	☐	Very satisfied

USE OF HEALTH SERVICES

3.1 Have you during the past 12 months visited?

	Yes	No	Number of times
General practitioner *(GP)*	☐	☐	☐☐
Emergency room	☐	☐	☐☐
Psychiatrist / Psychologist	☐	☐	☐☐
Another medical specialist than a general practitioner *(GP)* or a psychologist or psychiatrist *(not at a hospital)*	☐	☐	☐☐
Dentist / dental services	☐	☐	☐☐
Pharmacy *(to buy / get advice about medicines / treatment)*	☐	☐	☐☐
Physiotherapist	☐	☐	☐☐
Chiropractor	☐	☐	☐☐
Acupuncturist	☐	☐	☐☐
CAM provider *(homeopath, reflexologist, spiritual healer etc.)*	☐	☐	☐☐
Traditional healer *(helper, "reader" etc.)*	☐	☐	☐☐
Have you during the past 12 months communicated with any of the services above by using the Internet?	☐	☐	☐☐

3.2 Have you over the past 12 months visited a hospital?

	Yes	No	Number of times
Hospital admission	☐	☐	☐☐
Visited an out-patient clinic:			
Psychiatric out-patient clinic	☐	☐	☐☐
Other out-patient clinics (not psychiatric department)	☐	☐	☐☐

USE OF MEDICIN

4.1 **Do you use or have you used?** *Tick once for each line.*

	Never	Now	Previously, not now	Age first time
Blood pressure lowering drugs	☐	☐	☐	
Cholesterol lowering drugs	☐	☐	☐	
Diuretics	☐	☐	☐	
Drugs for heart disease *(for example anticoagulants, antiarrhythmics, nitroglycerin)?*	☐	☐	☐	
Insulin	☐	☐	☐	
Tablets for diabetes	☐	☐	☐	
Drugs for hypothyroidism (Levaxin or thyroxine)?	☐	☐	☐	

4.2 **How often during the past four weeks have you used?** *Tick once for each line.*

	Not used in the past 4 weeks	Less than every week	Every week but not daily	Daily
Painkillers on prescription	☐	☐	☐	☐
Painkiller non-prescription	☐	☐	☐	☐
Acid suppressive medication	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐

4.3 **State the name of all medicines, both those on prescription and non-prescription drugs, you have used regularly during the last 4 weeks.** *Do not include nonprescription vitamin-, mineral- and food supplements, herbs, naturopathic remedies etc.*

If there is not enough space for all medicines, continue on a separate sheet.

DIET

5.1 **Do you usually eat breakfast every day?**

☐ No ☐ Yes

5.2 **How many units of fruit or vegetables do you eat on average per day?** *One unit is by example one apple, one salad bowl.*

Number of units

5.3 **How often do you eat these food items?** *Tick once for each line.*

	0–1 times per month	2–3 times per month	1–3 times per week	4–6 times per week	Once a day or more
Red meat (*All products from beef, mutton, pork)?*	☐	☐	☐	☐	☐
Fruits, vegetables, and berries?	☐	☐	☐	☐	☐
Lean fish *(Cod, Saithe)?*	☐	☐	☐	☐	☐
Fat fish *(salmon, trout, redfish, mackerel, herring, halibut)?*	☐	☐	☐	☐	☐

5.4 **How many glasses / containers of the following do you normally drink / eat?** *Tick once for each line.*

	Rarely / never	1–6 glasses per week	1 glass per day	2–3 glass per day	4 or more per day
Milk / Yogurt with probiotics (Biola, Cultura, Activia, Actimel, BioQ etc.)	☐	☐	☐	☐	☐
Fruit juice	☐	☐	☐	☐	☐
Soft drinks with sugar	☐	☐	☐	☐	☐
Soft drinks with artificial sweeteners	☐	☐	☐	☐	☐

5.5 **How many cups of coffee or tea do you usually drink daily?** *Put 0 for the types you <u>do not</u> drink daily.*

	Number of cups
Filtered coffee	
Boiled coffee / french plunger coffee *(coarsely ground coffee for brewing)*	
Instant coffee	
Cups of espresso-based coffee *(from coffee-machines, capsules etc.)*	
Black tea *(e.g. Earl Grey, Black currant)*	
Green tea / white tea / oolong tea	
Herbal tea *(e.g. rose hip tea, chamomile tea, Rooibos tea)*	

HEALTH ANXIETY

	Not at all	A little bit	Moderately	Quite a bit	A great deal
6.1 **Do you think there is something seriously wrong with your body?**	☐	☐	☐	☐	☐
6.2 **Do you worry a lot about your health?**	☐	☐	☐	☐	☐
6.3 **Is it hard for you to believe the doctor when he / she tells you there is nothing to worry about?**	☐	☐	☐	☐	☐
6.4 **Do you often worry about the possibility that you have a serious illness?**	☐	☐	☐	☐	☐
6.5 **If a disease is brought to your attention (e.g., on TV, radio, the internet, the newspapers, or by someone you know), do you worry about getting it yourself?**	☐	☐	☐	☐	☐
6.6 **Do you find that you are bothered by many different symptoms?**	☐	☐	☐	☐	☐
6.7 **Do you have recurring thoughts about having a disease that is difficult to be rid ofom?**	☐	☐	☐	☐	☐

PHYSICAL ACTIVITY

7.1 **If you are in paid or unpaid work, which statement describes your work best?** *Tick the most apprioate box.*

- ☐ Mostly sedentary work? *(e.g. office work, mounting))*
- ☐ Work that requires a lot of walking *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting *(e.g. nursing, construction)*
- ☐ Heavy manual labour

7.2 **Describe your exercise and physical exertion in leisure time over the last year.** *If your activity varies throughout the year, give an average. Tick the most appropriate box.*

- ☐ Reading, watching TV / screen or other sedentary activity?
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week? (*including walking or cycling to place of work, Sunday-walking etc.)*
- ☐ Participation in recreational sports, heavy gardening, snow shoveling etc. at least 4 hours a week.
- ☐ Participation in hard training or sports competitions, regularly several times a week?

7.3 **During the last week, how much time did you spend sitting on a typical week or weekend day?** *E.g., at a desk, while visiting friends, while watching TV / screen.*

☐ Hours sitting on a weekday (both work and leisure hours*)*

☐ Hours on a weekend day

ALCOHOL

8.1 **How often do you drink alcohol??**

- ☐ Never
- ☐ Monthly or less frequently
- ☐ 2–4 times a month
- ☐ 2–3 times a week
- ☐ 4 or more times a week

8.2 **How many units of alcohol (1 beer, glass of wine or drink) do you usually drink when you drink alcohol?**

1–2	3–4	5–6	7–9	10 or more
☐	☐	☐	☐	☐

8.3 **How often do you have six or more units of alcohol in one occasion??**

- ☐ Never
- ☐ Less frequent than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

TOBACCO and SNUFF

9.1 **Do you / did you smoke daily?**

☐ Never ☐ Yes, now ☐ Yes, previously

9.2 **Have you used or do you use snuff or chewing tobacco daily?**

☐ Never ☐ Yes, now ☐ Yes, previously

QUESTIONS ABOUT CANCER

10.1 **Have you ever had**

	No	Yes	**If yes:** Age first time	**If yes:** Age last time
A mammogram	☐	☐		
Your PSA (Prostate Specific Antigen) level measured)	☐	☐		
A colon examination (colonoscopy, stool sample test)	☐	☐		

10.2 **Has anyone in your close <u>biological</u> family ever had**

	Children	Mother	Father	Maternal grandmother	Maternal grandfather	Paternal grandmother	Paternal grandfather	Aunt	Uncle	Sibling
Breast cancer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostate cancer	☐		☐		☐		☐		☐	☐
Colon cancer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

EDUCATION AND INCOME

11.1 **What is the highest levels of education you have completed?**
Tick one box only.

- ☐ Primary / partly secondary education. *(Up to 10 years of schooling)*
- ☐ Upper secondary education: *(a minimum of 3 years)*
- ☐ Tertiary education, short: College / university less than 4 years
- ☐ Tertiary education, long: College / university 4 years or more

11.2 **What was the household's total taxable income last year?**
Include income from work, social benefits and similar.

- ☐ Less than 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ More than 1 000 000 kr

FAMILY AND FRIENDS

12.1 **Who do you live with?**

	Yes	No	Number
Spouse / partner	☐	☐	
Other persons over 18 years	☐	☐	
Persons under 18 years	☐	☐	

12.2 **Do you have enough friends who can give you help and support when you need it?**

☐ Yes ☐ No

12.3 **Do you have enough friends that you can talk confidentially with?**

☐ Yes ☐ No

12.4 **How often do you take part in organised gatherings, e.g., sports clubs, political meetings, religious or other associations?**

Never, or just a few times a year	1–2 times a month	Approximately once a week	More than once a week
☐	☐	☐	☐

WOMAN ONLY

13.1 **How old were you when you first started menstruating?**

Age

13.2 **Are you pregnant at the moment?**

☐ No ☐ Yes ☐ Uncertain

13.3 **How many children have you given birth to?**

Number

13.4 **If you have given birth, how many months did you breast-feed? Fill in for each child the birth year, birth weight and the number of months breast feeding.** *Fill in the best you can*

	Birth year	Birth weight in grams	Months of breastfeeding
Child 1			
Child 2			
Child 3			
Child 4			
Child 5			
Child 6			

MEN ONLY

14.1 **Have you ever had an inflammation of your prostate / urine bladder?**

☐ No ☐ Yes

14.2 **Have you ever had a vasectomy?**

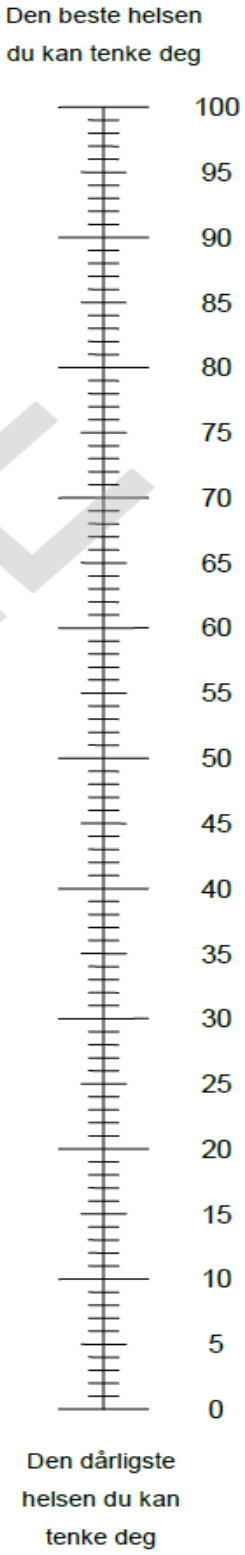
☐ No ☐ Yes **If yes:** Which year was it

Thank you for your contribution.

Appendix 3

Relevant questions from
Questionnaire 2 Tromsø 7

1.6 Fill in a number between 0 and 100 which best describes your current state of health



Number of

2.7 Biological children

2.11 Is your mother alive?

No Yes

If Yes, skip to 2.9.

If No:

2.11.1 What was your mother's age at death?

Age at death__

2.12 Is your father alive?

No Yes

If Yes, skip to 2.10.

If No:

2.12.1 What was your father's age at death?

Age at death__

3.15 How would you evaluate your finances?

Very good

Good

Average

Difficult

Very difficult

4 WORK

4.1 What is your main occupation/activity?

(Tick once or more)

Works full-time

Works part-time

Housekeeping

Retired

Disability benefit recipient/work assessment allowance

Family income supplement

Unemployed

Student/military service

4.2 I consider my occupation to have the following social status in society (if not currently employed, consider you latest occupation):

Very high social status

Fairly high social status

Neither high nor low social status

Fairly low social status

Very low status

5 ILLNESS AND WORRIES

Have you had any of the following illnesses or worries?

No Yes Age first time

5.1 Have you had coronary artery bypass surgery?

5.2 Have you had percutaneous coronary intervention?

5.3 Do you have or have you had claudicatio intermittens?

9 MEMORY

Please answer the questions below regarding your memory:

(Tick once for each line)

9.1 Has your memory declined?

No Yes

If No on 9.1-9.4, skip to 10.1.

If Yes on one or more on 9.1-9.4:

9.1.1 Is your memory a problem in your daily life?

No Yes

17 PAINKILLERS AND ANTIINFLAMMATORIC MEDICINES

17.1 Have you used analgesics and anti-inflammatory medication regularly in the past year? (i.e. acetylsalicylic acid, paracetamol, ibuprofen, diclofenac, naproxen)?

These include both over-the-counter and prescription only medicines, also including acetylsalicylic acid, which is used in low dosage as a blood thinning drug.

No Yes

If No, skip to 18.1.

If Yes:

Which analgesics and anti-inflammatory medication have your used the past year?

(Tick one or more)

17.1.1 «Baby» or low dose of Acetylsalicylic acid

(75 mg or 160 mg per tablet, i.e. Acetylsalicylic acid® i.e Albyl-E® Asasantin Retard®)

No Yes

18 MEDICINE INFORMATION

18.1 Have you used medicines (nonprescription and prescription) regularly during the last 4 weeks? Do not include dietary supplements (vitamins, minerals, omega-3, herbs or other natural remedies)

No Yes

If No, skip to 19.1.

If Yes:

Either because of forgetfulness, inconvenience or because they do not want to, it is common that people not always take the medicine they have been prescribed. The following questions concern your habits when taking *your* medicine.

18.1.14 How many times a week do you forget to take your medicines?

Less than once a week

Once a week

2-4 times a week

5 times a week or more

18.1.15 How many times a week do you decide to miss out your medicines?

Less than once a week

Once a week

2-4 times a week

5 times a week or more

19 PHYSICAL ACTIVITY

19.1 How often do you exercise?

(i.e. walking, skiing, swimming or training/sports)

Never

Less than once a week

Once a week

2-3 times a week

Approximately every day

If Never, skip to 20.1.

If >Never:

19.1.1 If you exercise - how hard do you exercise?

Easy - you do not become shortwinded or sweaty

You become shortwinded and sweaty

Hard - you become exhausted

19.1.2 For how long time do you exercise? (give an average)

Less than 15 minutes

15-29 minutes

30-60 minutes

More than 1 hour

20 FOOD HABITS

Do you use the following food supplements?

(Tick once for each line)

	No	Sometimes	Daily during the winter season	Daily
20.17 Cod liver oil or cod liver oil capsules				
20.18 Omega 3 capsules (fish oil, seal oil)				

As exact as you can, give an estimate of your alcohol habits. Keep the past year in mind when filling in.

31.1.1-*31.1.8.2*

9. Alkoholholdige drikker

Svar enten pr. måned eller pr. uke. Merk at porsjonsenhetene er forskjellige, 1/5 liter tilsvarer ett glass (2 dl), mens 1/3 liter tilsvarer 0,33 liter glassflaske/boks.

	Gang pr. måned			eller	Gang pr. uke				Mengde pr. gang						
	Aldri/ sjelden	1	2	3	1	2-3	4-5	6-7							
Øl, sterk øl, pils	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Lettøl	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Rusbrus, Cider m/alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1 ☐	1½ ☐	2+ ☐
Rødvin	☐	☐	☐	☐	☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hvitvin	☐	☐	☐	☐	☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hetvin (portvin, sherry o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(1 glass = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Brennevin, likør	☐	☐	☐	☐	☐	☐	☐	☐	(1 dram = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Blandede drinker, cocktail	☐	☐	☐	☐	☐	☐	☐	☐	(drink)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐

How often the past year have you:

Never Less than monthly Monthly Weekly Daily

31.1.1.9 Not been able to stop drinking alcohol when first started?
31.1.1.10 Failed to do what was normally expected from you because of drinking?
31.1.1.11 Needed alcohol in the morning to get yourself going after a heavy drinking session?
31.1.1.12 Had a feeling of guilt or remorse after drinking?
31.1.1.13 Been unable to remember what happened the night before because you had been drinking?
31.1.1.14 Drunk so much that you felt highly intoxicated (drunk)?

How often the past year have you:

Never Yes, but not during the past year Yes, during the past year

31.1.1.15 Have you or someone else been injured because of your drinking?
31.1.1.16 Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

DAILY SMOKING

33.1 Do you/did you smoke daily?

Never Yes, now Yes, previously

If Never, skip to 33.2

If Yes, now or Yes, previously

DAILY SMOKING

33.1.1 How old were you when you began smoking daily?

Age__

33.1.2 How many years in all have you smoked daily?

Number of years__

33.1.3 How many cigarettes do you or did you usually smoke per day?

Number of cigarettes ____

If Yes, previously on 33.1:

33.1.4 If you previously smoked daily, how long is it since you stopped?

Number of years__

OCCASIONAL SMOKING

33.2 Do you smoke, or have you smoked sometimes, but not daily?

Never Yes, now Yes, previously

If Never, skip to 33.3.

If Yes, now or Yes, previously:

OCCASIONAL SMOKING

33.2.1 How many cigarettes do you or did you usually smoke per day?

Number of cigarettes__

DAILY USE OF SNUFF

33.3 Have you used or do you use snuff or chewing tobacco?

Never Yes, now Yes, previously

If Never, skip to 33.4.

If Yes, now or Yes, previously?

DAILY USE OF SNUFF

33.3.1 How old were you when you began using snuff or chewing tobacco?

Age__

33.3.2 How many years in all have you used snuff or chewing tobacco?

Number of years____

33.3.3 If you use or have used snuff - how many portions do/did you take in a week?

Number of portions ____

If Yes, previously on 33.3:

DAILY USE OF SNUFF

33.3.4 If you used snuff daily previously, how many years since you stopped?

Number of years__

OCCASIONAL SNUFF USE

33.4 Do you use, or have you used snuff sometimes, but not daily?

Never Yes, now Yes, previously

If Never, skip to 34.1

If Yes, now or Yes, previously:

OCCASIONAL SNUFF USE

33.4.1 How many portions did you/do you usually take in a week?

Number of portions____

Appendix 4

Project approval from the Regional Committee for Medical and Health Research Ethics of North Norway

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			26.10.2015	2015/1775/REK nord
			Deres dato:	Deres referanse:
			22.09.2015	

Vår referanse må oppgis ved alle henvendelser

Marit Waaseth

2015/1775 Identifikasjon av faktorer som kan hindre optimal legemiddelbehandling hos personer med koronarsykdom i befolkningen

Forskningsansvarlig: UiT Norges arktiske universitet
Prosjektleder: Marit Waaseth

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 15.10.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektleders prosjektomtale
Informasjon om nytte og risiko ved legemiddelbehandlingen er viktig for å oppnå god etterlevelse, som igjen er viktig for å nå behandlingsmål. Prosjektet vil identifisere faktorer som hindrer optimal legemiddelbehandling. Det kan være faktorer knyttet til legemiddelbrukerne, f.eks. problemer med etterlevelsen grunnet bekymring for bivirkninger, eller det kan være at legemiddelregimet ikke er i henhold til behandlingsretningslinjene. Vi vil undersøke om oppnåelse av behandlingsmålene ved koronar hjertesykdom (blodtrykk, lipider og blodsukker) har sammenheng med - Legemiddelregime blant studiedeltakerne, samsvar med behandlingsretningslinjene - Legemiddelbrukernes etterlevelse, målt ved spørreskjema og ved reseptuttak - Deltakernes syn på legemiddelinformasjonen de har mottatt, bekymringer omkring legemiddelbruk og etterlevelse Med en svarprosent på 70 % og en prevalens av koronar hjertesykdom på 8,4 %, forventes at ca. 1900 av 23 000 deltakere i Tromsø 7 har koronarsykdom.

Vurdering

Design
Man ønsker å bruke data fra deltakere i Tromsø 7 som har koronarsykdom og har avgitt spørreskjemainformasjon, sosiodemografi, resultater fra analyser i biologisk materiale, antropometriske målinger og kliniske undersøkelser. Disse data ønskes koblet opp mot reseptregisteret.

Vurdering av om det avgitte samtykke er dekkende for koblingen
Det fremgår av det avgitte samtykket at det kan gjøres koblinger mot Reseptregisteret, og forsking på hjertesykdommer er et av hovedtema for Tromsøundersøkelsene. Komiteen anser således at det avgitte samtykket er dekkende for det som skal gjøres i studien.

Vedtak
Med hjemmel i helseforskningslovens §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2031, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:thrina.loennechen@uit.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Veronica Sørensen	77620758	31.05.2016	2015/1775/REK nord
			Deres dato:	**Deres referanse:**
			12.05.2016	

Vår referanse må oppgis ved alle henvendelser

Marit Waaseth
Universitetet i Tromsø

2015/1775 Identifikasjon av faktorer som kan hindre optimal legemiddelbehandling hos personer med koronarsykdom i befolkningen

Forskningsansvarlig institusjon: Institutt for farmasi
Prosjektleder: Marit Waaseth

Vi viser til søknad om prosjektendring datert 12.05.2016 for ovennevnte forskningsprosjekt. Søknaden er behandlet av REK nord på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
Vi viser til skjema for prosjektendring av 12.05.16 vedlagt revidert prosjektbeskrivelse.

Prosjektleder ber om å få utsatt startdato frem til 01.01.17. Bakgrunnen for dette skyldes at prosjektet ikke har fått nødvendige midler til oppstart.
REK har ingen innvendinger til dette.

Videre søkes om det om koble data fra Tromsø 7 opp mot Tromsøundersøkelsens endepunktsregister for kardiovaskulær sykdom. Registeret inneholder informasjon fra journaler ved Universitetssykehuset i Nord-Norge.

Vurdering av om samtykke for Tromsø 7 er dekkende for koblingen
I samtykkeskrivet for Tromsø 7 er det samtykket til kobling av de innsamlede data opp mot sentrale register, samt journaldata.

Ettersom endepunktsregisteret er et selvstendig register som inneholder journaldata, anser REK at den omsøkte kobling ligger godt innenfor det avgitte samtykke. Samtykkeskrivet er dekkende for den omsøkte kobling.

Etter fullmakt er det fatte slikt

Vedtak
Med hjemmel i helseforskningsloven § 11, godkjennes prosjektendringene.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen

er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Veronica Sørensen
Seniorrådgiver

Kopi til: *thrina.loennechen@uit.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Veronica Sørensen	77620758	07.03.2019	2015/1775/REK nord
			Deres dato:	**Deres referanse:**
			27.02.2019	

Vår referanse må oppgis ved alle henvendelser

Marit Waaseth
Universitetet i Tromsø

2015/1775 Identifikasjon av faktorer som kan hindre optimal legemiddelbehandling hos personer med koronarsykdom i befolkningen

Forskningsansvarlig institusjon: Institutt for farmasi, UiT - Norges arktiske universitet
Prosjektleder: Marit Waaseth

Vi viser til søknad om prosjektendring datert 27.02.2019 for ovennevnte forskningsprosjekt. Søknaden er behandlet av REK nord på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

Vi viser til skjema for prosjektendring av 27.02.19.

Endringen gjelder utvidelse av reseptuthenting fra ATC-gruppeC og B01AC06 til alle ACT koder, det søkes også om å gå lengre tilbake i tid. Omsøkte periode for uthenting av data for reseptuttak vil være fra 1.1.2004 til 31.12.2016.

REK legger til grunn at man fortsatt tar utgangspunkt i deltakere fra Tromsø 7 som har koronarsykdom og har avgitt spørreskjemainformasjon, sosiodemografi, resultater fra analyser i biologisk materiale, antropometriske målinger og kliniske undersøkelser og at det er disse data som ønskes koblet opp mot reseptregisteret.

Vurdering av om det avgitte samtykke er dekkende for koblingen
Det fremgår av det avgitte samtykket at det kan gjøres koblinger mot Reseptregisteret, og forsking på hjertesykdommer er et av hovedtema for Tromsøundersøkelsene. Komiteen anser således at det avgitte samtykket er dekkende for det som skal gjøres i studien.

REK har ingen innvendinger til den omsøkte endringen.

Vedtak
Med hjemmel i helseforskningsloven § 11 godkjennes prosjektendringen.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningsloven § 10 og forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Veronica Sørensen
seniorrådgiver

Kopi til: *thrina.loennechen@uit.no; postmottak@uit.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Maren Johannessen Melsbø	77620748	20.06.2019	2015/1775/REK nord
			Deres dato:	**Deres referanse:**
			17.06.2019	

Vår referanse må oppgis ved alle henvendelser

Marit Waaseth
Universitetet i Tromsø

2015/1775 Identifikasjon av faktorer som kan hindre optimal legemiddelbehandling hos personer med koronarsykdom i befolkningen

Forskningsansvarlig institusjon: Institutt for farmasi, UiT - Norges arktiske universitet
Prosjektleder: Marit Waaseth

Vi viser til søknad om prosjektendring datert 17.6.2019. Søknaden er behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) ved sekretariatsleder, etter fullmakt gitt av komiteen med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Vurdering
Prosjektleder opplyser i endringssøknaden at endringen gjelder inklusjon av 2 nye prosjektmedarbeidere, herunder en ph.d.-student og en mastergradsstudent. Endringen er begrunnet med at *«noen må gjøre analysene slik at prosjektet kommer godt i havn.»*

REK har ingen innvendinger til den omsøkte endringen. Det forutsettes at prosjektet til mastergradsstudenten ligger innenfor formålet til hovedprosjektet 2015/1775.

Etter fullmakt er det fattet slikt

Vedtak
Med hjemmel i helseforskningsloven § 11 godkjennes prosjektendringen.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Klageadgang
Du kan klage på REKs vedtak, jf. helseforskningsloven § 10 og forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Til informasjon bytter REK søknadsportal i sommer. Den nye portalen vil være klar i august. Se våre hjemmesider under «Aktuelle meldinger» for oppdatert informasjon.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Maren Johannessen Melsbø
rådgiver

Kopi til: *thrina.loennechen@uit.no; postmottak@uit.no*

Appendix 5

Data Protection Impact Assessment
from UiT The Arctic University of Norway

NSD – Personvernkonsekvensvurdering

Prosjektopplysninger

Prosjekttittel: Barriers to optimal medication therapy and treatment goal achievement among persons with coronary heart disease

Behandlingsansvarlig: Universitetet i Tromsø

Prosjektansvarlig: Marit Waaseth

Prosjektnummer 56818

Om konsekvensvurdering (DPIA)

NSD har gjennomgått innholdet i meldeskjemaet. Det er vår vurdering at den planlagte behandlingen av personopplysninger vil innebære relativt høy risiko for de registrertes rettigheter og friheter, og dermed krever en personvernkonsekvensvurdering (DPIA), jf. personvernforordningen art. 35.

Dette fordi den planlagte behandlingen av personopplysninger innebærer:

- Behandling av særlige kategorier av personopplysninger
- Behandling av personopplysninger i stor skala (stort antall registrerte, mengde opplysninger og lang varighet)
- Sammenstilling av datasett

På oppdrag fra UiT sin ledelse, har NSD i samråd med prosjektansvarlig og rådgivere ved institusjonen laget utkast til en DPIA som inneholder:

1) En systematisk beskrivelse av den planlagte behandlingen av personopplysninger.
2) Vurdering av om behandlingsaktivitetene er nødvendige og står i rimelig forhold til formålene.
3) Analyse av risiko for de registrertes rettigheter og friheter.
4) Planlagte tiltak for å håndtere risikoene.

Ved å følge de planlagte tiltakene, mener NSD at personvernrisikoen er redusert i en slik grad at behandlingen kan gjennomføres i samsvar med personvernforordningen, uten forhåndsdrøfting med Datatilsynet.

Behandlingsansvarlig institusjon (v/ledelsen) bestemmer om personvernkonsekvensvurderingen er tilfredsstillende utført, og om personvernrisikoen er redusert til et akseptabelt nivå slik at behandlingen kan gjennomføres, eller om det er nødvendig med forhåndsdrøfting (se del 6 – Ledelsens beslutning). Dette etter å ha rådført seg med sitt personvernombud og tatt hensyn til eventuelle adferdsnormer. Vi oversender derfor vår vurdering til UiT og personvernombud for godkjenning. NSD ber om å få tilsendt endelig versjon av DPIA med ledelsens beslutning i signert form.

Dersom behandling av personopplysninger igangsettes på grunnlag av DPIA, og deretter endres, minner vi om at endringene kan medføre behov for ny eller oppdatert DPIA. Prosjektansvarlig skal melde endringer til NSD, og institusjonen har ansvar for å påse at dette skjer. NSD vil ta kontakt hvert annet år. Ved melding om endringer i prosjektet, vil NSD bistå i vurderingen av om ny DPIA er nødvendig og utfører i så fall denne i samråd med UiT sin ledelse og personvernombud.

Følgende personer har deltatt i personvernkonsekvensvurderingen:

Navn	Rolle/funksjon	Virksomhet
Trine Anikken Larsen	Seniorrådgiver	NSD Norsk senter for forskningsdata
Marit Waaseth	Prosjektleder og hovedveileder for PhD-student	UiT Norges arktiske universitet
Elisabeth Pedersen	PhD-stipendiat og daglig ansvarlig	UiT Norges arktiske universitet
Anne Elise Eggen	Vitenskapelig leder for den sjuende Tromsøundersøkelsen og biveileder for stipendiaten	UiT Norges arktiske universitet
Joakim Bakkevold	Personvernombud	UiT Norges arktiske universitet

Personvernkonsekvensvurdering - DPIA

1. Systematisk beskrivelse av planlagte behandlingsaktiviteter og formål

Her følger en ren beskrivelse av den planlagte behandlingen av personopplysninger, slik den er oppgitt i meldeskjema med vedlegg. Vurdering av behandlingen følger i del 2 og 3.

1.1 Bakgrunnen for DPIA i prosjektet

Prosjektet fikk konsesjon av Datatilsynet i vedtak datert 14.03.2018. I etterkant av konsesjonsvedtaket har prosjektansvarlig ønsket å legge til variabelen ApotekKonsesjonNr fra Reseptregisteret. Variabelen forteller hvor mange apotek deltakerne benytter seg av.

På grunn av en uklar formulering fra NSD sin side ble det oppfattet slik at kun personer med hjerte- og karsykdom skulle inngå som en del av utvalget, det vil si cirka 1800 personer. Dette ble også lagt til grunn i konsesjonsvedtaket fra Datatilsynet. Prosjektansvarlig ønsker imidlertid å benytte data fra samtlige av deltakerne fra den syvende runden av Tromsøundersøkelsen (Tromsø 7), det vil si til sammen 21 083 personer.

Sammenholdt med at prosjektet behandler særlige kategorier (sensitive) personopplysninger om helse, at prosjektet har lang varighet (31.12.2030) og at utvalget består av en stor andel registrerte innebærer at det må utføres en DPIA for hele prosjektet.

1.2 Formål

Formålet med prosjektet er å identifisere faktorer som hindrer optimal legemiddelbehandling. Det kan være faktorer knyttet til legemiddelbrukerne, f.eks. problemer med etterlevelsen grunnet bekymring for bivirkninger, eller det kan være at legemiddelregimet ikke er i henhold til behandlingsretningslinjene. Forskerne vil derfor undersøke om oppnåelse av behandlingsmålene ved koronar hjertesykdom (blodtrykk, lipider og blodsukker) har sammenheng med:

- Legemiddelregime blant studiedeltakerne, samsvar med behandlingsretningslinjene
- Legemiddelbrukernes etterlevelse, målt ved spørreskjema og ved reseptuttak
- Deltakernes syn på legemiddelinformasjonen de har mottatt, bekymringer omkring legemiddelbruk og etterlevelse.

1.3 Registrerte

Utvalget består av deltakere fra den syvende runden av Tromsøundersøkelsen (Tromsø 7). Dette vil totalt utgjøre 21 083 personer.

1.4 Type og omfang personopplysninger

Prosjektet innebærer behandling av alminnelige personopplysninger og behandling av særlige kategorier (sensitive) personopplysninger om helse.

Fra Tromsøundersøkelsen hentes det følgende opplysninger: Dato for deltakelse, sosiodemografi (fødselsår, kjønn, utdanning, jobbsituasjon), selvrapportert sykdom, plager og helsetilstand, legemiddelbruk, bruk av helsetjenester, livsstil (diett, røyk/snus, alkohol, fysisk aktivitet), familieforhold, behov for legemiddelinformasjon (type informasjon mottatt, hjelp til å ta medisin, informasjonsbehov), bekymringer angående legemidler, selvrapportert etterlevelse (glemmer/lar være å ta medisin), generell helsebekymring, antropometriske målinger (høyde, vekt, blodtrykk) og analyser i biologisk materiale (glukose, lipider). Det vises til detaljert variabelliste fra Tromsøundersøkelsen, se vedlegg 1.

Fra Reseptregisteret hentes det opplysninger om følgende:

- Forskriver: Fødselsår, kjønn, profesjon og spesialitet*
- Pasient: Fødselsdato
- Resept/ordinasjon: Utleveringsdato, utsalgspris og totale antall, reseptkategori, hjemmel og refusjonspunkt iht. blåreseptforskrift
- Legemiddel: Produktnavn, informasjon om legemiddelets styrke, enheter og dosering, ATC-koder, varegrupper, tidspunkt for utlevering og apotekets utsalgspriser
- I tillegg innhentes variabelen ApotekKonsesjonNr som var søkt i opprinnelig konsesjonssøknad til Datatilsynet i 2018, se vedlegg 3.

Det vises til detaljert variabelliste fra Reseptregisteret, se vedlegg 2.

1.5 Datakilder

Data skal hentes fra følgende registre: Tromsøundersøkelsen og Reseptregisteret. Opplysningene er samlet inn og administrert av Universitetet i Tromsø og FHI, og disse institusjonene vil utlevere data etter kontrakt.

1.6 Hvordan personopplysningene skal behandles

Behandling av personopplysninger innebærer sammenstilling/kobling av data. Allerede innhentede opplysninger fra Tromsø 7 undersøkelsen vil sammenstilles med utvalgte variabler fra Reseptregisteret. Utlevering og sammenstilling vil skje i henhold til Universitetet i Tromsø og FHI sine rutiner.

1.7 Dataflyt: Lagringsenheter, kanaler for sending/deling, koblingsprosedyre

Opplysningene er samlet inn og administrert av Universitetet i Tromsø og Folkehelseinstituttet (FHI), og disse institusjonene utleverer data til forskere etter kontrakt.

Datafilene i Tromsøundersøkelsen oppbevares i EUTRO. EUTRO-personell klargjør filene, sender dem til Reseptregisteret for kobling og utleverer dem til forskerne etter at koblingen er foretatt. Forskerne får utlevert filer uten personnummer, personlige koder i

Tromsøundersøkelsen (perskey) eller koder som gjør at det mulig å identifisere personer eller koble filene til andre datamaterialer.

Kobling av data vil skje i henhold til FHI/Reseptregisterets rutine for sammenstilling som etablert av FHI, se følgende nettside: https://www.fhi.no/contentassets/70fca3dd291041e18bab6660509f5252/arbeidsbeskrivelse-reseptregisteret-28112018.pdf

Etter at sammenstillingen er utført vil koblingsnøkkelen oppbevares av SSB.

Overføring av forskningsfiler fra Tromsøundersøkelsen følger oppsatte retningslinjer. Et fildelingsprogram med passordbeskyttelse (Uninett Filesender 2.0) vil bli brukt for å sende filene over internett.

Filen (avidentifisert) vil bli levert til stipendiaten (Elisabeth Pedersen) etter Reseptregisterets prosedyrer, og hun vil jobbe med den på sin universitets-PC ved Institutt for farmasi, og ha den lagret på sitt universitetsserverområde. Eventuell videreformidling av data i filen vil kun skje til andre prosjektmedarbeidere (navngitt i dokumentet) ved hjelp av universitetets system for sikker filoverføring (dvs. med passord). For de fleste av medarbeiderne vil det være lite aktuelt å ha tilgang til dataene direkte. Hovedsakelig er det prosjektansvarlig og statistikerne (Frode Skjold og Raul Primicerio) som vil ha tilgang til data etter avtale med stipendiaten og ved sikker filoverføring fra henne. De andre vil kun få tabellresultater fra analysene til felles tolkning/vurdering.

Det skal kun foretas én kobling. Dette innebærer at data hentes ut kun én gang fra både Tromsøundersøkelsen og Reseptregisteret.

1.8 Hvem vil få tilgang til personopplysninger?

I dette prosjektet vil følgende kategorier av mottakere ha tilgang til personopplysninger: Elisabeth Pedersen, Marit Waaseth, Anne Elise Eggen, Beate H. Garcia, Lars Småbrekke, Kjell H. Halvorsen, Frode Skjold og Raul Primicerio.

1.9 Varighet

Prosjektperioden er satt frem til 31.12.2030. Prosjektdata vil slettes ved prosjektslutt.

Datamaterialet må være tilgjengelig inntil alle artiklene i doktorgradsprosjektet er publisert, men opplysningene skal ikke oppbevares for videre forskning etter prosjektslutt.

1.10 Tillatelser/dispensasjon

REK har vurdert at prosjektet faller innenfor helseforskningslovens virkeområde (referansenummer 2015/1775). REK har i vedtak av 26.10.2015 (vedlegg 4), samt senere vedtak om prosjektendring datert 31.05.2016, godkjent prosjektet (vedlegg 5).

2. Vurdering av om behandlingsaktivitetene er nødvendige og står i rimelig forhold til formålene

Prosjektets formål er å identifisere faktorer som hindrer optimal legemiddelbehandling. Det kan være faktorer knyttet til legemiddelbrukerne, f.eks. problemer med etterlevelsen grunnet bekymring for bivirkninger, eller det kan være at legemiddelregimet ikke er i henhold til behandlingsretningslinjene. Det skal undersøkes om oppnåelse av behandlingsmålene ved koronar hjertesykdom (blodtrykk, lipider og blodsukker) har sammenheng med:

- Legemiddelregime blant studiedeltakerne, samsvar med behandlingsretningslinjene
- Legemiddelbrukernes etterlevelse, målt ved spørreskjema og ved reseptuttak
- Deltakernes syn på legemiddelinformasjon de har mottatt, bekymringer omkring legemiddelbruk og etterlevelse

Utvalget hentes fra Tromsø 7 som er en delstudie under Tromsøundersøkelsen, og innbefatter personer med hjerte- og karsykdommer. Tromsøundersøkelsen er en prospektiv, populasjonsbasert helseundersøkelse som startet i 1974. Mer enn 45 000 personer har deltatt i en eller flere av de syv rundene av undersøkelsene som er gjennomført. Den store oppslutningen har sikret kvaliteten på helseundersøkelsen og de vitenskapelige resultatene.

NSD vurderer samfunnsnytten i prosjektet til å være vesentlig og at behandlingsaktivitetene er nødvendige og står i rimelig forhold til formålene.

2.1 Rettslig grunnlag for behandling av personopplysninger

Prosjektet er basert på samtykke fra deltakerne i Tromsøundersøkelsen. Lovlig grunnlag for behandlingen vil dermed være den registrertes uttrykkelige samtykke, jf. personvernforordningen art. 6 nr. 1 a) og art. 9 nr. 2 bokstav a), jf. personopplysningsloven § 10.

Av informasjonsskrivet fremgår det at kan forskes på hjerte- og karsykdommer, og at opplysningene kan kobles mot Reseptregisteret. NSD vurderer informasjonsskrivet til å gi god og tydelig informasjon om hva deltakelse i prosjektet innebærer og hvilke rettigheter de registrerte har.

2.2 Formålsbegrensning

Formålet med behandlingen vurderes til å være spesifikk, uttrykkelig angitt og berettiget. Deltakerne har avgitt et bredt samtykke i forbindelse med deltakelse i Tromsøundersøkelsen. I informasjonsskrivet er det lagt opp til mulige koblinger mot ulike helseregistre i fremtiden. Så fremt denne koblingen gjøres i tråd med formålet som er beskrevet i prosjektet, vurderer NSD dette til at personopplysninger ikke viderebehandles til nye/andre formål som vurderes å være uforenelige med det opprinnelige forskningsformålet.

2.3 Dataminimering

NSD vurderer at personopplysningene som behandles i prosjektet er adekvate, relevante, nødvendige og begrenset til det som er nødvendig for formålet med behandlingen (dataminimering).

For begrunnelser for variabler fra Tromsøundersøkelsen vises det her til vedlegg 2.

Som begrunnelse for variabler som innhentes fra Reseptregisteret angir forskergruppen følgende:

Forskriveropplysninger: Pasientforholdet og medication adherence kan tenkes å være påvirket av forskrivende leges spesialitet, alder og kjønn. Opplysningene vil bli benyttet i multivariate analyser, f.eks. korrespondanseanalyse, for å utforske og muligens identifisere adherencemønstre hos pasienter hos de ulike legegruppene. Profesjonsopplysningene vil benyttes for å ekskludere forskrivere som ikke er leger.

Pasient: Informasjon om dødsmåned/år er nødvendig for å kunne ekskludere deltakere ved dødsfall, siden de ellers vil kunne fremstå som om de har avsluttet behandlingen, det vil si feilaktig tolkes som dårlig etterlevelse/adherence.

Legemiddelopplysninger: Opplysningene anses nødvendige for vurdering av legemiddelbruk opp mot spørsmålene i Tromsøundersøkelsen.

Variabelen ApotekKonsesjonNr: Variabelen angir hvor mange apotek deltakerne benytter seg av. Tidligere studie har funnet ut at antall apotek pasienten forholder seg til kan påvirke adherence, og forskerne ønsker å undersøke om dette også kan være tilfelle i dette prosjektet.

2.4 Lagringsbegrensning

Prosjektperioden er begrenset til å vare frem til 31.12.2030. Tidsperioden vurderes å være begrenset til det som er nødvendig for å gjennomføre prosjektet. Datamaterialet skal slettes ved prosjektslutt.

2.5 Personopplysningssikkerhet

Kobling av data fra Reseptregisteret vil skje i henhold til FHI sine etablerte rutiner for sammenstilling som etablert av FHI.

Overføringen av forskningsfiler fra Tromsøundersøkelsen følger oppsatte retningslinjer. Et fildelingsprogram med passordbeskyttelse (Uninett Filesender 2.0) brukes til å sende filene over internett. Når forskerne mottar filene vil disse oppbevares på en datamaskin beskyttet med brukernavn og passord. Denne er også sikret bak institusjonens brannmur. Forskningsfilene vil oppbevares på en datamaskin i nettverkssystem så lenge dataene analyseres. Tilgangen til datamaterialet er begrenset til åtte personer som er nevnt under punkt 1.9.

NSD vurderer dette til å være gode tiltak for å ivareta personopplysningssikkerheten i prosjektet.

2.6 De registrertes rettigheter og friheter

Personvernforordningen gir den registrerte en rekke rettigheter (art. 12-22). Behandlingsansvarlig har plikt til å informere den enkelte registrerte om behandlingen og tilrettelegge for at den registrerte kan utøve sine rettigheter. Rettighetene gjelder så lenge det behandles personopplysninger og det er mulig sikkert å identifisere den registrerte.

I dette prosjektet vil deltakerne ha krav på å benytte seg av sin rett til innsyn, retting, sletting, begrensning og dataportabilitet. De registrerte kan utøve sine rettigheter ved å kontakte Tromsøundersøkelsen, hvorav kontaktinformasjon er oppgitt på prosjektets nettsted.

3. Vurdering av risiko for de registrertes rettigheter og friheter

NSD vil trekke frem konkrete risikoer i prosjektet:

- Prosjektet vil behandle særlige kategorier av personopplysninger (sensitive opplysninger) om helseforhold.
- Det skal innhentes data fra et stort utvalg (21 083 personer).
- Prosjektet innebærer behandling av personopplysninger over lang tid (31.12.2030).

4. Planlagte tiltak for å håndtere risikoene

4.1 Tiltak

- Data skal kun hentes ut én gang i løpet av prosjektperioden.
- Tilgangen til datamaterialet er begrenset til en mindre gruppe med personer.
- Sammenstilling av data fra Reseptregisteret skjer i henhold til Reseptregisterets rutine og koblingsnøkkel skal oppbevares av SSB.
- Det ferdig koblede datamaterialet skal oppbevares på datamaskin beskyttet med brukernavn og passord, og i tillegg bak virksomhetens brannmur.
- Forskningsfilene skal oppbevares på en datamaskin i virksomhetens nettverkssystem så lenge dataene er under analyse.

4.2 Vurdering fra eget personvernombud

Personvernombud (PVO) Joakim Bakkevold har kontrollert gjennomføringen av vurderingen av personvernkonsekvenser i henhold til GDPR artikkel 35. Etter personvernombudets vurdering medfører behandlingen av personopplysninger i prosjektet en høy risiko for de registrerte personers rettigheter og friheter og da i hovedsak deres personvernrettigheter. Det skal behandles i stor skala opplysninger som faller inn under særlige kategorier,

helseopplysninger, som i utgangspunktet er forbudt, jf. GDPR artikkel 9 nr. 1. Behandlingen skal også foregå over lang tid.

Vurderingen av personvernkonsekvensene inneholder en systematisk beskrivelse av den planlagte behandlingen av personopplysninger. Den inneholder en vurdering av om behandlingsaktivitetene er nødvendige og står i rimelig forhold til formålene. Den inneholder en analyse av risiko for de registrerte rettigheter og friheter og planlagte tiltak for å håndtere risikoene. Slik personvernombudet vurderer gjennomføringen av vurderingen av personvernkonsekvenser, så er den i tråd med kravene til innhold etter GDPR artikkel 35.

Personvernombudet gir følgende råd:

Prosjektet er vurdert av Datatilsynet etter tidligere personvernlovgivning og registrert hos NSD i det gamle meldingsarkivet. Behandlingsansvarlig representert av NSD bør oppdatere protokollbeskrivelsen av prosjektet, slik at den innholdsmessig blir i tråd med GDPR artikkel 30.

Behandlingsansvarlig bør klargjøre hvilke av universitetets systemer, nettverk og maskiner som skal benyttes i prosjektet til behandling og lagring av data. Dernest vurdere om disse er tilstrekkelig sikret i tråd med risikoen for de registrerte.

Behandlingsansvarlig bør vurdere spesielt om omfanget, her antall registrerte, av behandlingen av personopplysninger i prosjektet er i tråd med prinsippet om dataminimering. Datatilsynet har i sin vurdering lagt til grunn at studiet omfatter cirka 1 800 registrerte. Det riktige er 21 083.

5. NSD sin samlede vurdering av personvernet

NSD vurderer på grunnlag av ovennevnte tiltak at prosjektet håndterer de identifiserte risikoene på en akseptabel måte, og at personvernet således er tilstrekkelig ivaretatt.

6. Godkjenning fra institusjonens ledelse

Universitetsledelsen vil påpeke at tidligere konsesjon gitt av Datatilsynet var basert på feilaktig antall registrerte. Det presiseres at dette ikke har betydning for denne vurderingen, siden dette er en selvstendig vurdering som ikke bygger på Datatilsynets konsesjon.

Ledelsen beslutter og begrunner:

- DPIA er godkjent/validert: Behandlingen kan starte opp, under følgende forutsetninger:
    1. NSD må oppdatere protokollinformasjon om prosjektet
    2. Filen med komplett datagrunnlag (de 21 083 personene) må ha ekstra sikring ut over det som følger av hjemmeområdet (H:\), slik som kryptering

3. Denne filen, og eventuelle uttrekk fra denne, kan kun åpnes på UiT-eide maskiner som har kryptert harddisk

Dato	Versjon av DPIA	Godkjent elektronisk av (henhold til fullmakt)
6.2.2019	1.0	Gøril Heitmann, ass. universitetsdirektør

Vedlegg:
1. Variabelliste fra Tromsøundersøkelsen + begrunnelse for variabler
2. Variabelliste fra Reseptregisteret
3. Endringsmelding for variabel fra Reseptregisteret
4. REK-vedtak forhåndsgodkjenning
5. REK-vedtak endringsmelding
6. Informasjon fra prosjektleder om behandling av data
7. Meldeskjema