FACULTY OF HEALTH SCIENCES, AARHUS UNIVERSITY, DENMARK

Research Year Report

Impact of comorbidity on the prediction of first-time myocardial infarction, stroke, or death from single-photon emission computed tomography myocardial perfusion imaging: A Danish cohort study

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Preface

This research year report is based on a study carried out during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark from 1 September 2012 to 31 August 2013.

I would like to express my sincere gratitude to my main supervisor Henrik Toft Sørensen for sharing his extensive knowledge, for being truly engaged in my work throughout the year, and for letting me work with a new clinical database.
In addition, I would like to thank him for giving me the opportunity to do research at California Pacific Medical Center Research Institute (CPMCRI) in San Francisco for three months during Spring 2013. It has been a great experience – both intellectual as well as personal to me. Special thanks goes to Karin Lottrup Petersen and the rest of the people at CPMCRI for a very warm welcome and a pleasant stay.

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Astrid Blicher Schelde

Abbreviations list

aHR	Adjusted hazard ratio
CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
CI	Confidence interval
DNPR	Danish National Patient Registry
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
SPECT	Single-photon emission computed tomography

Contents

Extract

Introduction

Single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) is a non-invasive technique used to assess myocardial perfusion (1) and thereby detect coronary artery disease (CAD) (1).

The age distribution of the population is changing with a growing proportion of elderly (2). Increased life expectancy and sedentary lifestyles increase the prevalence of chronic medical conditions (3). Currently, 45% of the adult population and 90% of persons older than 65 years in the US have at least one chronic condition (4). Since the greatest risk of CAD exists among the elderly (5), an increasing number of patients suspected with CAD also have other co-existing diseases, *i.e.*, comorbidities (6-8). As CAD shares risk factors with many chronic diseases, such as diabetes, chronic pulmonary disease, and obesity (7-9), the prevalence of comorbidity further increases among patients with CAD. Although the usefulness of SPECT MPI in predicting future coronary events has been shown previously (1, 10), no studies have examined the impact of comorbidity level.

We therefore conducted a cohort study to examine the long-term risk of myocardial infarction (MI), stroke, and all-cause death associated with a normal *vs.* abnormal SPECT MPI in patients without previous MI and cerebrovascular disease, and to assess the impact of comorbidity level.

Methods

Setting

The Danish National Health Service provides free, universal, tax-supported healthcare, guaranteeing all residents unrestricted access to general practitioners and hospitals (11). Unambiguous individual-level linkage between medical databases was performed using the ten-digit Danish civil personal registration number assigned to each Danish citizen at birth and to residents upon immigration (12).

Study population

We conducted this cohort study using the MPI database at Aarhus University Hospital, Skejby (13). Since 1 January 1999, the MPI database has collected information on all SPECT

MPI procedures performed at Aarhus University Hospital (13). We used this database to identify all adult Danish citizens (≥ 18 years of age) without previous MI or cerebrovascular disease, who had a ^{99m}Tc-sestamibi SPECT MPI performed from 1 January 1999 through last date of registration to the database on 26 April 2011 (13). For each patient, we identified the first SPECT MPI in the study period. The database includes the following variables: sex, age, and scan result. A normal scan was defined as a scan without defects, while an abnormal scan was defined by the presence of a reversible and/or fixed defect.

Comorbidity burden

We obtained information on comorbid conditions from inpatient and outpatient clinic hospital diagnoses recorded in the Danish National Patient Registry (DNPR) (14) in the 10 years preceding the SPECT MPI procedure. The DNPR includes data on dates of admission and discharge from all non-psychiatric hospital admissions in Denmark since 1977 and from emergency room and outpatient clinical visits since 1995 (14). One primary diagnosis and up to several secondary diagnoses are provided for each hospital contact, classified according to the *International Classification of Diseases* 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter (14). We assessed comorbidity level by means of the widely used Charlson Comorbidity Index (CCI) (15). We computed the total CCI score for each patient, and then categorized the study population according to comorbidity burden: score of 0 (normal), score of 1 (moderate), and score ≥ 2 (severe). Because we excluded all patients with MI and cerebrovascular disease, these diseases did not contribute to the CCI. The ICD codes for conditions included in the CCI are provided in Appendix 1.

Myocardial infarction, stroke, and death

We used the DNPR to identify all first-time inpatient admissions for MI and stroke (ischemic or hemorrhagic stroke) following a SPECT MPI procedure during the study period. The ICD codes are provided in Appendix 2.

We obtained information on mortality from the Danish Civil Registration System (16). This registry contains data on date of birth, residence, date of emigration, and exact date of any death for the entire Danish population since 1968, with daily electronic updates (16).

Statistical analysis

We followed all patients from the date of the outpatient SPECT MPI procedure or discharge from the admission during which the SPECT MPI procedure was performed (2 patients died

during admission and were excluded) until the date of an outcome, death, emigration, 10 years of follow-up, or 31 December 2011, whichever came first. We characterized patients according to sex, age, and comorbidity.

We used a cumulative incidence method to compute 10-year risk of MI, stroke, and all-cause death, and illustrated graphically the 10-year cumulative incidence function of each outcome: For MI and stroke, we used the proportional subhazards model by Fine and Gray (17). For all-cause mortality, we used the Kaplan-Meier estimator. Death was considered a competing risk in all analyses of non-fatal outcomes. We computed the risk and incidence rate for each outcome within 0−30 days, 31−365 days, and 1−10 years of follow-up, overall and by comorbidity levels. We used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome and stratified on comorbidity levels and the two most prevalent individual CCI conditions in the study population (diabetes and chronic pulmonary disease). We adjusted for categories of sex, age (18−49, 50−59, 60−69, and ≥70 years), and comorbidity level.

We performed two sensitivity analyses to examine the influence of 1) including only MI and stroke outcomes during an acute admission; and 2) including all-available information on comorbid conditions in the DNPR (back to its establishment in 1977).

The assumption of proportional hazards was assessed graphically and was found to be appropriate. All statistical analyses were performed using STATA software version 12.0.

The study was approved by the Danish Data Protection Agency (j.no. 2011-41-6772).

Results

Patient characteristics

We identified 7,382 patients without previous MI or cerebrovascular disease and with a first-time SPECT MPI in the study period. Among the patients, 5,062 (69%) had a normal scan and 2,320 (31%) an abnormal scan (Table 1). A total of 27 patients (0.4%) emigrated after a median follow-up time of 1.8 years. Women accounted for a greater proportion of the patients with a normal scan (63%) compared with an abnormal scan (39%). The median age was 61 years among patients with a normal scan and 65 years among patients with an abnormal scan (Table 1).

Patients with normal scans were more likely to have low comorbidity (64%) compared with patients with abnormal scans (51%), and less likely to have moderate comorbidity (20%

vs. 24%) and severe comorbidity (16% *vs*. 25%). Also, they were less likely to have diabetes (10% *vs.* 15%) and chronic pulmonary disease (11% *vs.* 14%) (Table 1).

Myocardial infarction, stroke, and all-cause death

We identified 351 first-time hospitalizations for MI, 290 first-time hospitalizations for stroke, and 835 deaths within a maximum of 10 years of follow-up. Risk estimates within 0-30 days, 31-365 days, and 1-10 years are provided in Appendix 3. The overall 10-year risk of MI was 5.7% (95% CI: 4.7 to 6.8) in patients with a normal scan and 11.7% (95% CI: 10.1 to 13.4) in patients with an abnormal scan (Table 2). The corresponding adjusted hazard ratio (aHR) during this 10-year period comparing an abnormal scan with a normal scan was 1.86 (95% CI: 1.50 to 2.32) (Table 2).

For stroke, the 10-year risk was 6.2% (95% CI: 5.2 to 7.4) in patients with a normal scan and 8.3% (95% CI: 6.8 to 9.9) among those with an abnormal scan (Table 2). No substantial association was observed between an abnormal scan and stroke (aHR=1.11; 95% CI: 0.87 to 1.42) (Table 2).

The sensitivity analyses including only outcomes during an acute admission showed an increased aHR for MI (aHR=1.96; 95% CI: 1.53 to 2.50) and a slightly increased aHR for stroke (aHR=1.23; 95% CI: 0.94 to 1.61) (Appendix 4).

Ten-year mortality risk in patients with a normal scan was 16.5% (95% CI: 14.7 to 18.5) and 31.0% (95% CI: 28.3 to 33.8) in patients with an abnormal scan (Table 2). The aHR for all-cause death comparing an abnormal scan with a normal scan was 1.48 (95% CI: 1.29 to 1.71) (Table 2).

Comorbidity

Among patients with low comorbidity, 10-year risk according to normal *vs*. abnormal scans was 4.2% *vs*. 9.5% for MI, 5.1% *vs*. 7.2% for stroke, and 10.0% *vs*. 19.1% for all-cause death (Table 3). This risk increased to 6.4% *vs*. 13.6% for MI, 5.7% *vs*. 10.1% for stroke, and 22.7% *vs*. 38.6% for all-cause death in patients with moderate level of comorbidity, and 10.8% *vs*. 14.5% for MI, 11.0% *vs*. 8.9% for stroke, and 34.3% *vs*. 49.4% for all-cause death in patients with severe comorbidity (Table 3). Increasing level of comorbidity was associated with increasing risk of MI and all-cause death within 31-365 days and 1-10 years (Appendix 5).

The aHR comparing an abnormal scan with a normal scan in categories of normal, moderate, and severe comorbidity was 2.07 (95% CI: 1.48 to 2.90), 1.84 (95% CI: 1.22 to

2.79), and 1.62 (95% CI: 1.08 to 2.42) for MI, and 1.39 (95% CI: 1.08 to 1.78), 1.39 (95% CI: 1.07 to 1.80), and 1.56 (95% CI: 1.24 to 1.97) for all-cause death (Table 3). Compared with patients without diabetes (aHR=1.80; 95% CI: 1.42 to 2.28), diabetes increased the risk prediction of MI (aHR=2.43; 95% CI: 1.32 to 4.49). Diabetes did not modify the association between the scan result and all-cause death. Chronic pulmonary disease did not modify the association between the scan result and MI or all-cause death (Table 4).

For stroke, the data supported no consistent modification of the aHRs according to normal, and severe comorbidity level, while the risk of stroke was modified in patients with moderate comorbidity (aHR=1.87; 95% CI: 1.13 to 3.07) (Table 3). The sensitivity analysis revealed no substantial change in the estimates when comparing a 10-year comorbidity assessment with an all-available approach (Appendix 6).

Discussion

In this cohort study we found that, compared to patients with a normal SPECT MPI scan, patients with an abnormal scan were at increased risk for MI and all-cause death within 10 years after the procedure, but not at substantial risk for stroke. Importantly, the risk prediction for MI and all-cause death was consistent for all patients independent of their comorbidity level.

Study strengths and limitations

Several issues should be considered when evaluating our findings. The main strength of this study includes the large study population. Because the Danish Health Care Service provides tax-supported universal healthcare for every Danish citizen, selection bias is practically eliminated. The diagnostic accuracy of SPECT MPI for detecting CAD has recently been demonstrated (18) with test sensitivity (88%) exceeding specificity (61%) (18). However, since our study examines the risk of future adverse outcomes following SPECT MPI, and not the risk of adverse outcomes associated with underlying CAD, this will not affect study results.

Recorded diagnoses in the DNPR have been validated, yielding a positive predictive value of approximately 90% for MI (19), >75% for stroke (20), and 98% for CCI conditions overall (21). Any potential misclassification of the outcome diagnoses in the DNPR is likely independent of the scan result (*i.e.*, nondifferential), and thus cannot explain the increased

HRs for MI and all-cause death. The mortality data are complete (16). Some of the diseases in the CCI, such as diabetes and chronic pulmonary disease are likely to be under-recorded in the DNPR, because some patients are treated in primary care only. However, any potential under-recording of comorbidities is unlikely to explain the increased HRs of MI and all-cause mortality associated with different comorbidity levels.

Although we took several potential confounders into account, such as sex, age, and comorbidity level, we cannot exclude unmeasured confounding from life style factors (*e.g.* smoking, diet, and exercise). Due to the non-randomized design, unknown confounding can never be excluded.

Comparison with other studies

Few previous studies have examined the risk of MI and all-cause death as single end points following SPECT MPI procedure comparing a normal *vs*. abnormal scan (22, 23). Vanzetto *et al.* (22) included 1,137 patients with low to intermediate risk of cardiac events and who all underwent exercise stress tests. This study reported an adjusted odds ratio of 4.20 (95% CI: 1.93 to 9.14) for MI for 1 or 2 abnormal segments on SPECT MPI, and 4.97 (95% CI: 2.15 to 11.49) for ≥ 3 abnormal segments, both compared with a normal scan (22). The magnitude of the association was thus more than two times higher than ours (22). Importantly, the previous study used another nuclear tracer (Thallium) and different exclusion criteria, excluding patients over the age of 75 years, or patients who underwent revascularization procedures within 3 months before or after the imaging procedure.

Risks of all-cause death comparing an abnormal scan with a normal scan (23) in a previous study were similar to our results, with relative risk increases between 70%−80% (23).

No previous studies have examined the risk of stroke associated with the result from a SPECT MPI scan.

Although we did not observe a substantial association with stroke, it should be noted that a small increased risk of approximately 20% cannot be ruled out as indicated by the sensitivity analysis.

In contrast to previous studies, we examined the risk of adverse outcomes according to different levels of comorbidity. Our findings indicate that the prediction of MI and all-cause death is practically independent of the patient's comorbidity level. This has different research and clinical implications: 1) When studying relative risk of MI and all-cause death following SPECT MPI procedure in patients with normal *vs*. abnormal scans, it is not necessary to

stratify on comorbidity levels; 2) Also, this indicates that the impact of an abnormal scan can be applied to a broad patient population with different levels of comorbidity.

No studies have examined the SPECT MPI risk prediction in subgroups of patients with chronic pulmonary disease or the risk of MI as a single end point in patients with diabetes. Only one study has examined the mortality risk prediction among diabetic patients (24). Consistent with our results, this study associated a reversible defect with a 1.9-fold increased mortality risk (95% CI: 1.2 to 2.6) compared with patients with a normal SPECT MPI scan (24).

Conclusions

Independently of comorbidity level, an abnormal SPECT MPI scan predicted the 10-year risk of MI and all-cause death, but not stroke.

Abstract

Objectives: To examine the association between a normal *vs.* abnormal single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) scan on 10-year risk of myocardial infarction (MI), stroke, and all-cause death, overall and according to comorbidity level.

Background: The impact of comorbidity on the prediction from SPECT MPI remains unclear.

Methods: We identified all patients without previous MI or cerebrovascular disease who had a SPECT MPI performed at Aarhus University Hospital-Skejby during 1999-2011. For each patient, we identified the first SPECT MPI in the study period and categorized this as normal (no defects) or abnormal (reversible and/or fixed defects). Using nationwide medical registries, we obtained information on comorbidity level (using Charlson Comorbidity Index) and outcomes. We used Cox regression to compute hazard ratios (HRs) adjusting for sex, age, and comorbidity level.

Results: Among 7,382 patients, 5,062 (69%) had normal scans and 2,320 (31%) abnormal scans. Patients with a normal *vs*. abnormal scan had a 10-year risk of 5.7% *vs*. 11.7% for MI, 6.2% *vs*. 8.3% for stroke, and 16.5% *vs*. 31.0% for all-cause death. Compared with a normal scan, an abnormal scan predicted the risk of MI (adjusted HR=1.86, 95% CI: 1.50 to 2.32) and all-cause death (1.48, 95% CI: 1.29 to 1.71), but not stroke (1.11, 95% CI: 0.87 to 1.42). Comorbidity level did not affect substantially the association between the scan result and MI (adjusted HR: 2.07 [95% CI: 1.48 to 2.90] for normal comorbidity, 1.84 [95% CI: 1.22 to 2.79] for moderate comorbidity, and 1.62 [95% CI: 1.08 to 2.42] for severe comorbidity) or all-cause death (adjusted HR: 1.39 [95% CI: 1.08 to 1.78], 1.39 [95% CI: 1.07 to 1.80], and 1.56 [95% CI: 1.24 to 1.97], respectively).

Conclusions: In patients without previous MI or cerebrovascular disease, an abnormal scan predicted independent of comorbidity level the 10-year risk of MI and all-cause death, but not stroke.

Dansk resume

Formål: Formålet med dette kohortestudie var at undersøge sammenhængen mellem en normal *vs.* abnormal myokardieskintigrafi og risikoen for myokardieinfarkt, slagtilfælde og død i løbet af 10 år både overordnet set samt i forhold til komorbiditetsniveau.

Baggrund: Myokardieskintigrafis evne til at estimere risikoen for myokardieinfarkt, slagtilfælde og død er ikke tidligere undersøgt hos patienter med forskellig grader af komorbiditet.

Metode: Vi inkluderede alle voksne patienter (≥ 18 år) uden tidligere myokardieinfarkt eller cerebrovaskulær sygdom med en førstegangs-myokardieskintigrafi foretaget på Aarhus Universitetshospital, Skejby i perioden 1999-2011. En normal scanning var defineret ved ikke at have defekter, mens en abnormal scanning havde reversible eller irreversible defekter. Vi indhentede information vedrørende komorbiditet samt udfald ved hjælp af nationale medicinske registre. Komorbiditetsniveauer blev defineret som normal, moderat og svær baseret på Charlson's komorbiditetsindex. Vi benyttede Cox regression til at beregne hazard ratioer justeret for køn, alder og komorbiditetsniveau.

Resultater: Ud af 7.382 patienter havde 5.062 (69%) patienter en normal scanning, mens 2.320 (31%) patienter havde en abnormal scanning. Tiårsrisikoen for patienter med en normal *vs.* abnormal scanning var 5,7% *vs.* 11,7% for myokardieinfarkt, 6,2% *vs.* 8,3% for slagtilfælde samt 16,5% *vs.* 31,0% for død. Efter justering, svarede dette til 86% øget risiko for myokardieinfarkt og 48% øget dødelighed hos patienter med en abnormal scanning. Komorbiditetsniveau havde ingen betydelig effekt på sammenhængen med myokardieinfarkt og død. Der var ingen betydelig øget risiko for slagtilfælde.

Konklusion: En abnormal myokardieskintigrafi prædikterede førstegangstilfælde af myokardieinfarkt og død uafhængigt af komorbiditetsniveau, men ikke slagtilfælde.

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Supplementary information

Introduction

SPECT MPI procedure

Reduced blood supply to the myocardium due to atherosclerosis, is referred to as coronary artery disease (CAD). Single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) is a non-invasive and safe nuclear medicine procedure that is used to assess myocardial perfusion (1) and thus diagnose CAD (1). With a SPECT MPI procedure, a nuclear tracer is injected into the blood stream, carried to, and taken up by vascularized myocardium, and visualized by a camera that senses gamma rays released by the tracer (25). In that way, SPECT MPI assesses the myocardial blood flow in the different coronary domains (25).

The SPECT MPI procedure is often performed as a combination of a stress, and a rest scan to evaluate, if there are any signs of reversible ischemia, irreversible ischemia, or a combination of both (13). The rest scan will only take place if the stress scan shows abnormalities (25).

The stress scan takes place with the patient undergoing different types of stressors to increase the workload of the heart, and aim to show the blood supply of the coronary arteries at peak exertion. Stress is applied either physically on a treadmill, or pharmacologically using vasodilating (*e.g.*, adenosine or dipyridamole) or inotropic drugs (*e.g.*, dobutamine) (13).

Important clinical indications for SPECT MPI include detection of CAD in patients with moderate risk of CAD, and in patients with moderate risk of CAD with an inconclusive treadmill electrocardiogram (26). To be at moderate risk of CAD, the patient must fulfill two of the three following criteria: 1) Retrosternal chest pain less than 15 minutes; 2) Provocation of cheat pain due to physical activity, coldness, or emotional stress; 3) Alleviation of chest pain by rest or nitroglycerine (26) .

In addition, the procedure is used in patients with CAD shown on coronary angiography, but where doubt exists about the hemodynamic significance of a coronary artery stenosis (26). On this basis, SPECT MPI can assist to differentiate between patients, who may benefit from medical therapy or revascularization procedures (27).

Methods

Study design

The aim of this study was to examine the association between a normal *vs.* abnormal scan (exposure) on long-term risk of myocardial infarction (MI), stroke, and all-cause death (outcome), both overall and according to comorbidity level. We therefore aimed to calculate the cumulative incidence proportion (risk) for each outcome in each of the two result groups, and then compare the incidence rate (specifically, the hazard ratio (HR)) in the two groups.

To achieve these aim, we designed a cohort study. With a cohort study, it is possible to follow a cohort for a long time period, even though the patients in the cohort not necessarily enter the study at the same time, or later is censored during follow-up due to emigration. Typically, a cohort study comprises two cohorts (exposed and unexposed), who are followed for a certain period of time, with the aim of comparing the risks in the two cohorts (28).

Study population

We used a MPI database to identify all adult Danish citizens (≥ 18 years of age) with a SPECT MPI procedure performed between 1 January 1999 and 26 April 2011 at Aarhus University Hospital, Skejby (13). For each patient, we identified the first SPECT MPI in the study period.

The MPI database was established in 1999 as a local clinical database. Aarhus University Hospital, Skejby has performed the procedures since the establishment of Department of Clinical Physiology and Nuclear Medicine in 1992 (13). Because we were only interested in estimating the risk of first-time events associated with a scan result (*i.e.*, risk and not prognostic impact), we excluded all patients with a previous history of MI and cerebrovascular disease in the ten years preceding the SPECT MPI procedure.

Start of follow-up

For each patient, follow-up began on the day of the outpatient clinic visit or discharge from the inpatient admission during which the SPECT MPI procedure was performed. Exact date of MI and stroke diagnoses during admission is unknown, and by starting follow-up at discharge day instead of admission day, we eliminated potential bias (immortal time bias) arising from long admission time, in which period patients are without risk of the outcomes (28).

Information on comorbidity

We used the Danish National Patient Registry (DNPR) to obtain information on recorded comorbid conditions from inpatient and outpatient clinic hospital diagnoses (14)

We assessed comorbidity level using the Charlson Comorbidity Index (CCI) (15), which originally was developed in 1984 to predict 1-year mortality in hospitalized medical patients from a list of 19 diseases that are weighted according to their severity (15). This scoring system assigns between 1 and 6 points to 19 conditions (1 point for MI, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes without end organ damage; 2 points for hemiplegia, moderate to severe renal disease, diabetes with end organ damage, non-metastatic solid tumor, leukaemia, and lymphoma; 3 points for moderate to severe liver disease; 6 points for metastatic cancer and AIDS). The sum of points serves as a measure of the burden of comorbidity.

The CCI has subsequently been adapted to databases (29), and registration of the diagnoses from the CCI have been validated in Denmark (21). The included diseases in the CCI are presented in Figure A.

Figure A. Charlson Comorbidity Index

Weights	Conditions
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes without end organ damage
2	Hemiplegia
	Moderate to severe renal disease
	Diabetes with end organ damage
	Non-metastatic solid tumor
	Leukaemia
	Lymphoma
3	Moderate to severe liver disease
6	Metastatic cancer
	AIDS

In the primary analysis, we chose to obtain information on comorbid conditions registered in the DNPR in the ten years preceding SPECT MPI procedure to ensure a uniform collection of information for each patient.

Sensitivity analyses

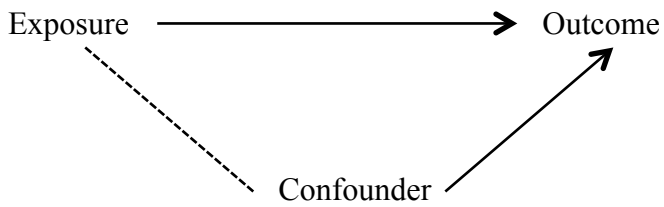
We performed two secondary sensitivity analyses. In the first analysis we addressed the potential difference of including MI and stroke diagnoses during an *acute* inpatient admission *vs.* including MI and stroke diagnoses obtained during *any* inpatient admission. In the second analysis we addressed the potential difference of using all-available comorbidity information in the DNPR (back to its establishment in 1977) *vs.* a fixed look-back window (10 years), based on a new study by Brunelli *et al* (30). In the first analysis, we adjusted for sex, age, and comorbidity level. In the second analysis, we adjusted for sex and age.

Confounding and effect measure modification

Confounding

When we are dealing with different co-variables, some of them may be confounders. Confounding is a systematic error, leading us to mix or confuse the effect of an exposure with the effect of another variable; the confounder (28).

By definition, a confounder has to be associated with the exposure (SPECT MPI). Also, the confounder must increase the risk of the outcome (MI, stroke, all-cause death) in the unexposed, and is thus a good predictor/marker for the outcome, but not necessarily the cause. Furthermore, the confounder must not be on the causal path between the exposure and the outcome (28). The relationship between exposure, outcome, and the confounder is illustrated below.



There are different types of confounding; residual confounding, unknown confounding, unmeasured confounding, and confounding measured and adjusted for.

If a variable you have chosen to control for is divided into too broad categories, there may be confounding within them, *i.e.,* residual confounding. To avoid residual confounding, it can be desirable to divide the data into more categories, but not too fine since this can result in too

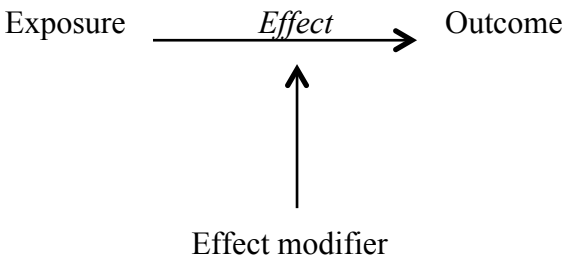
few events within each category, and hence imprecise estimates. Furthermore, residual confounding can be introduced, if a co-variable that are adjusted for is measured imprecise (28).

Unknown confounding represents en error due to a variable with no knowledge about. Unmeasured confounding is when we know a variable is a confounder, but we do not have information about it.

Confounding should be dealt with in the study design by restricting, matching, or randomizing, or in the analyses by stratifying, standardization, or in regression analyses (28). In our study, we adjusted for sex, age, and comorbidity level based on prior knowledge.

Effect measure modification

Effect measure modification occurs, when another factor modifies the association between exposure and the outcome (28), illustrated below.



It is present, when an exposure-outcome relationship is different within different levels of a variable, *e.g.,* difference in the relationship between smoking and cardiac death among males and females. If a specific variable is an effect measure modifier, the relation between exposure and outcome should be presented for each level of the variable.

Results

The overall primary results are presented in the extract. Below, the results from the two secondary sensitivity analyses will be presented.

Patient characteristics

Among the 7,382 patients, a total of 4,165 (56%) had normal comorbidity, 1,626 (22%) had moderate, and 1,591 (22%) had severe comorbidity based on comorbidity information measured back to 1977 (Appendix 7). Based on comorbidity information obtained 10 years back, 4,460 (60%), 1,552 (21%), and 1,370 (19%) had normal, moderate, and severe comorbidity, respectively (Table 1).

According to information on comorbidity back to 1977, patients with a normal *vs.* abnormal scan were more likely to be with low comorbidity (60% *vs.* 47%), and less likely to be with moderate (21% *vs.* 25%), and severe (19% *vs.* 28%) comorbidity (Appendix 7). Also, they were less likely to have diabetes (10% *vs.* 15%), and chronic pulmonary disease (13% *vs.* 15%) (Appendix 7).

These results were consistent with the results based on a fixed 10-year time window approach where patients with a normal *vs.* abnormal scan had low (64% *vs.* 51%), moderate (20% *vs.* 24%), and severe (16% *vs.* 25%) comorbidity, and a history of diabetes (10% *vs.* 15%) and chronic pulmonary disease (11% *vs.* 14%) (Table 1).

The total proportions of the two most prevalent individual CCI conditions in the study population according to information on comorbidity back to 1977 (12% for diabetes and 13% for chronic pulmonary disease) (Appendix 7) were consistent with the results based on a fixed 10-year time window (11% for diabetes and 12% for chronic pulmonary disease) (Table 1). However, the total prevalence when measuring information on comorbidity back to 1977 *vs.* a fixed 10-year time window was higher for both diabetes (855 *vs.* 842) and for chronic pulmonary disease (991 *vs.* 886), showing that not all of these diagnoses were captured with a fixed 10-year time window.

Myocardial infarction and stroke

We identified 284 first-time hospitalizations for MI and 229 for stroke during an *acute* inpatient admission. The 10-year risk was 4.4% (95% confidence interval (CI): 3.6 to 5.4) for MI, and 4.8% (95% CI: 3.9 to 5.8) for stroke among patients with a normal scan, and 9.9%

(95% CI: 8.4 to 11.5) for MI, and 6.8% (95% CI: 5.5 to 8.4) for stroke among patients with an abnormal scan (Appendix 4).

Based on inclusion of MI and stroke diagnoses during *any* inpatient admission, we identified 351 first-time hospitalizations for MI and 290 for stroke. The 10-year risk estimates was 5.7% (95% CI: 4.7 to 6.8) for MI, and 6.2% (95% CI: 5.2 to 7.4) for stroke in patients with a normal scan, and 11.7% (95% CI: 10.1 to 13.4) for MI, and 8.3% (95% CI: 6.8 to 9.9) for stroke among patients with an abnormal scan (Table 2), indicating that the risk estimates tended to be higher based on an inclusion of MI and stroke diagnoses during *any* inpatient admission compared with inclusion of these diagnoses during an *acute* inpatient admission.

When including diagnoses of MI and stroke during an *acute* admission, the adjusted HR (aHR) within 10 years comparing a normal *vs.* abnormal scan was 1.96 (95% CI: 1.53 to 2.50) for MI and 1.23 (95% CI: 0.94 to 1.61) for stroke (Appendix 4), showing a slightly elevation compared with the aHR based on inclusion of MI and stroke diagnoses during *any* admission with estimates of 1.86 (95% CI: 1.50 to 2.32) for MI and 1.11 (95% CI: 0.87 to 1.42) for stroke (Table 2).

Comorbidity

Stratified on comorbidity level measured back to 1977 in patients with a normal *vs.* abnormal scan, 10-year risk was 4.0% *vs.* 9.2% for MI, 4.8% *vs.* 6.8% for stroke, and 9.3% *vs.* 17.4% for all-cause death in patients with normal comorbidity (Appendix 6). In patients with moderate comorbidity, the risk estimates increased to 6.8% *vs.* 14.3% for MI, 5.5% *vs.* 10.4% for stroke, and 21.2% *vs.* 38.2% for all-cause death. Patients with severe comorbidity had ten-year risk estimates of 9.8% *vs.* 13.9% for MI, 10.5% *vs.* 9.1% for stroke, and 34.2% *vs.* 49.5% for all-cause death (Appendix 6).

According to a fixed 10-year time window, patients with a normal *vs.* abnormal scan with normal comorbidity had 10-year risks of 4.2% *vs.* 9.5% for MI, 5.1% *vs.* 7.2% for stroke, and 10.0% *vs.* 19.1% for all-cause death, increasing in patients with moderate comorbidity to 6.4% *vs.* 13.6%, 5.7% *vs.* 10.1%, and 22.7% *vs.* 38.6% for MI, stroke, and all-cause death, respectively (Table 3). Patients with severe comorbidity with a normal *vs.* abnormal scan had ten-year risk estimates of 10.8% *vs.* 14.5% for MI, 11.0% *vs.* 8.9% for stroke, and 34.3% *vs.* 49.4% for all-cause death (Table 3). A comparison between these risk estimates according to level of comorbidity including data on comorbidity since 1977 *vs.* a fixed 10-year time window revealed no substantial differences.

The corresponding aHR during the same 10-year time period comparing a normal *vs.* abnormal scan according to level of comorbidity measured back to 1977 in patients with normal, moderate, and severe comorbidity was 2.20 (95% CI: 1.55 to 3.13), 1.74 (95% CI: 1.16 to 2.62), and 1.65 (95% CI: 1.12 to 2.44) for MI, 1.06 (95% CI: 0.73 to 1.54), 1.92 (95% CI: 1.17 to 3.14), and 0.80 (95% CI: 0.51 to 1.23) for stroke, and 1.32 (95% CI: 1.01 to 1.72), 1.44 (95% CI: 1.11 to 1.88), and 1.58 (95% CI: 1.27 to 1.97) for all-cause death (Appendix 6).

The aHR based on a fixed 10-year time window in patients with normal, moderate, and severe comorbidity was 2.07 (95% CI: 1.48 to 2.09), 1.84 (95% CI: 1.22 to 2.79), and 1.62 (95% CI: 1.08 to 2.42) for MI, 1.03 (95% CI: 0.72 to 1.46), 1.87 (95% CI: 1.13 to 3.07), and 0.82 (95% CI: 0.51 to 1.32) for stroke, and 1.39 (95% CI: 1.08 to 1.78), 1.39 (95% CI: 1.07 to 1.80), and 1.56 (95% CI: 1.24 to 1.97) for all-cause death (Table 3), showing no overall difference compared with the estimates based on an all-available approach (Appendix 6).

Discussion

Study strengths and limitations

The main strength of this study includes a large study population. The cohort study design is within a Danish free, tax-supported health care system setting, which practically removed selection bias.

Positive predictive values of outcome diagnoses, and comorbidity in the DNPR have been reported to be as high as 90% for MI (19), >75% for stroke (20), and 98% overall for Charlson comorbidities (21). We assume that any errors or differences in coding practice of the outcome data are independent of the scan result (*i.e.* non-differential), and therefore, if anything, would bias the estimates toward the null value (28). Mortality data are complete (16). Some of the diseases in the CCI, such as diabetes and chronic pulmonary disease are likely to be under-recorded in the DNPR, since some patients are treated in primary care only. However, this cannot explain the increased aHRs of MI and all-cause death associated with different levels of comorbidity.

In this study, we adjusted for sex, age, and comorbidity level. Unmeasured confounding, including life style factors such as smoking, exercise, and diet cannot be excluded.

Moreover, since our study design is non-randomized, we cannot exclude unknown confounding.

An all-available *vs*. a fixed 10-year time window

The consideration behind an all-available time window approach is to measure information on comorbidity more completely and thus avoid introducing residual confounding (28). Furthermore, the diseases in the CCI are predominantly chronic conditions, which could affect the result of a SPECT MPI scan many years after first diagnosis.

The argument for choosing a fixed time window of 10 years is to avoid including conditions that the patient may already be cured of, such as cancer. Of note, this approach also capture comorbidity diagnosed more than 10 years ago if the patient had at least one in- or outpatient (primary or secondary) diagnosis registered within the last 10 years. Finally, a fixed look-back time window results in a uniform collection of information for each patient.

A previous study compared estimation for dichotomous variables using all-available covariate information *vs.* information from a fixed historical window (30). Brunelli *et al* (30)

reported that an all-available time window approach resulted in a less biased estimate compared with a fixed time window.

When working with a fixed time window, it may be difficult to determine an appropriate length. In this cohort study, the sensitivity analyses revealed no substantial changes in the estimates when comparing an all-available time window with a fixed 10-year time window approach. This indicates that a window of 10 years for this study was appropriate.

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Figures

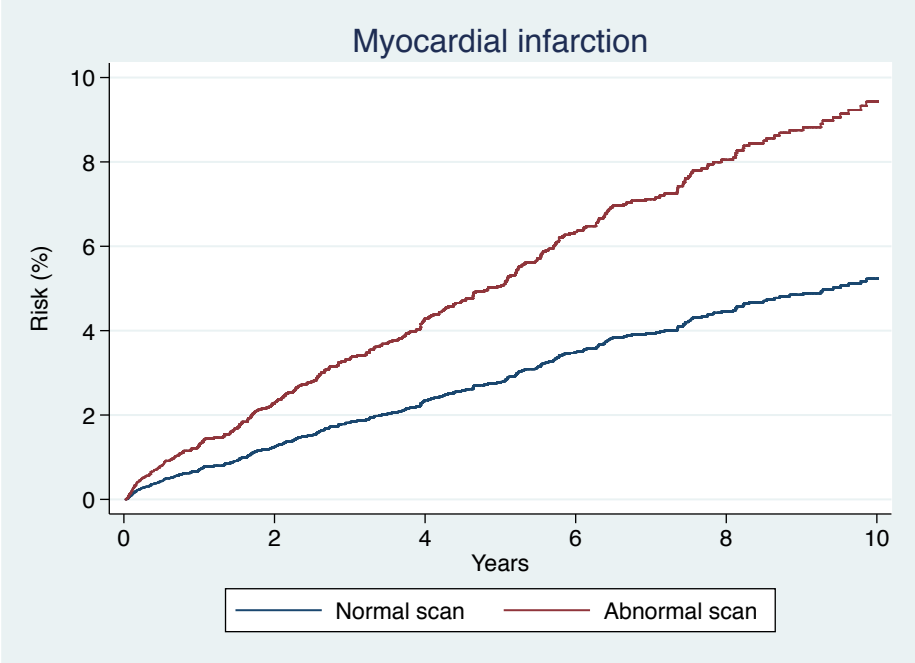

Fig 1a. Cumulative incidence (risk) of first-time hospitalization for myocardial infarction among patients with normal and abnormal scans.

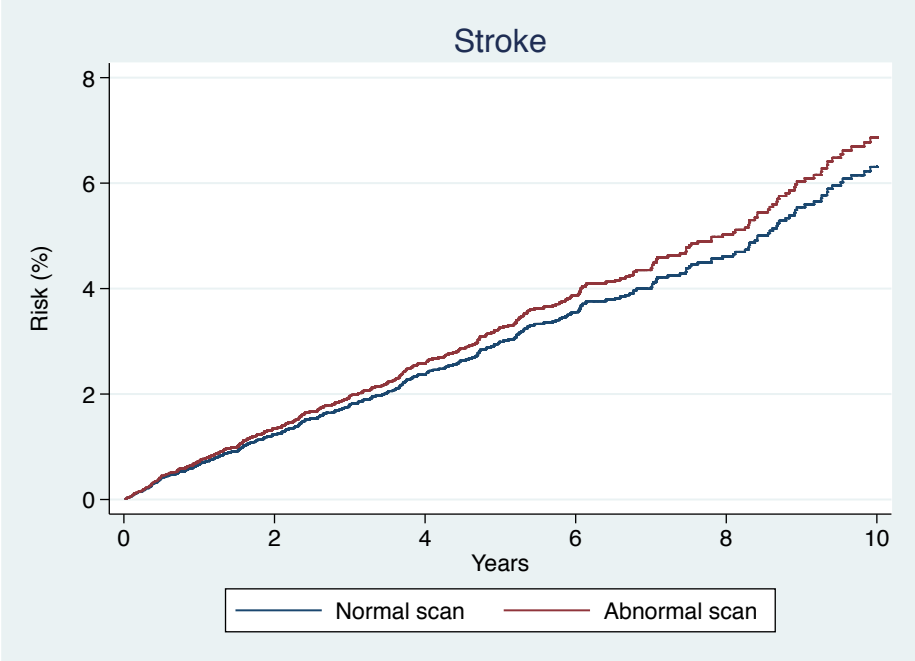

Fig 1b. Cumulative incidence (risk) of first-time hospitalization for stroke among patients with normal and abnormal scans.

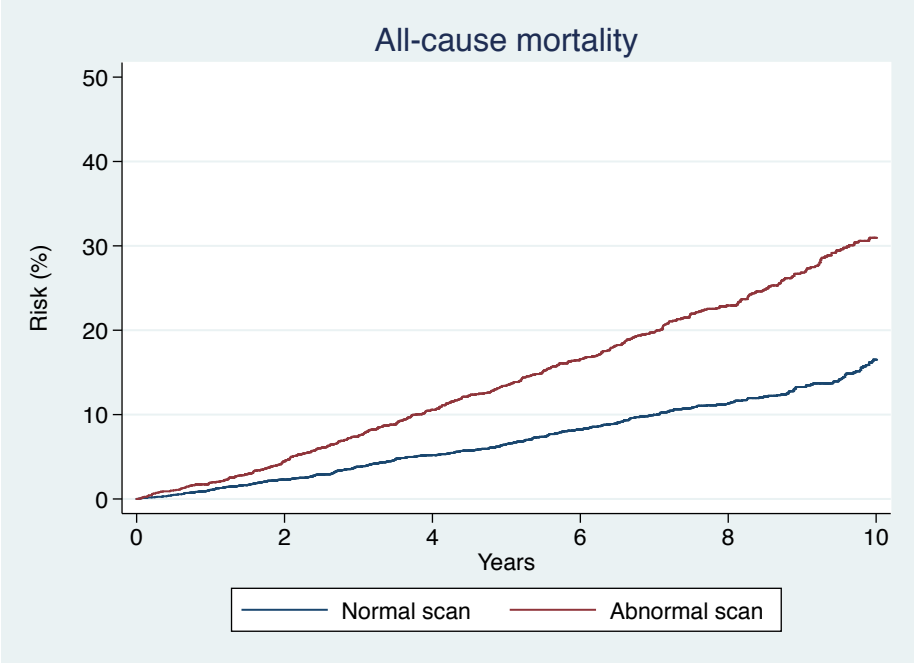

Fig 1c. Cumulative mortality risk among patients with normal and abnormal scans.

Tables

Table 1. Patients with normal and abnormal scans by sex, age, and comorbidity obtained in the 10 years preceding SPECT MPI.

	Normal scan (n=5,062)	Abnormal scan (n=2,320)	Total (n=7,382)
Sex			
Female	3,170 (63%)	913 (39%)	4,083 (55%)
Male	1,892 (37%)	1,407 (61%)	3,299 (45%)
Age (years)			
18−49	970 (19%)	269 (12%)	1,239 (17%)
50−59	1,473 (29%)	556 (24%)	2,029 (27%)
60−69	1,512 (30%)	740 (32%)	2,252 (31%)
≥ 70	1,107 (22%)	755 (32%)	1,862 (25%)
Median age (years)	61	65	62
Comorbidity level*			
Normal	3,270 (64%)	1,190 (51%)	4,460 (60%)
Moderate	1,002 (20%)	550 (24%)	1,552 (21%)
Severe	790 (16%)	580 (25%)	1,370 (19%)
Frequent individual comorbidites			
Diabetes	489 (10%)	353 (15%)	842 (11%)
Chronic pulmonary disease	565 (11%)	321 (14%)	886 (12%)

*Levels of comorbidity were based on Charlson Comorbidity Index scores as follows: 0 (normal), 1 (moderate), and ≥ 2 (severe)

Table 2. Risk and hazard ratio of myocardial infarction, stroke, and all-cause death within 10 years following a normal vs. abnormal scan.

	Scan result	No. of events	Risk % (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Myocardial infarction	Normal	157	5.7 (4.7 to 6.8)	1 (reference)	1 (reference)
	Abnormal	194	11.7 (10.1 to 13.4)	2.52 (2.04 to 3.11)	1.86 (1.50 to 2.32)
Stroke	Normal	170	6.2 (5.2 to 7.4)	1 (reference)	1 (reference)
	Abnormal	120	8.3 (6.8 to 9.9)	1.38 (1.10 to 1.75)	1.11 (0.87 to 1.42)
All-cause death	Normal	397	16.5 (14.7 to 18.5)	1 (reference)	1 (reference)
	Abnormal	438	31.0 (28.3 to 33.8)	2.11 (1.84 to 2.42)	1.48 (1.29 to 1.71)

*Adjusted for sex, age, and comorbidity level

Table 3. Risk and hazard ratio of myocardial infarction, stroke, and all-cause death within 10 years following a normal vs. abnormal scan according to comorbidity level obtained in the 10 years preceding SPECT MPI.

Comorbidity level	Scan result	No. of events	Risk % (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Normal (0 points)					
Myocardial infarction	Normal	70	4.2 (3.2 to 5.5)	1 (reference)	1 (reference)
	Abnormal	79	9.5 (7.5 to 11.7)	2.71 (1.96 to 3.74)	2.07 (1.48 to 2.90)
Stroke	Normal	93	5.1 (4.0 to 6.4)	1 (reference)	1 (reference)
	Abnormal	52	7.2 (5.3 to 9.5)	1.30 (0.93 to 1.83)	1.03 (0.72 to 1.46)
All-cause death	Normal	138	10.0 (8.1 to 12.2)	1 (reference)	1 (reference)
	Abnormal	131	19.1 (16.1 to 22.5)	2.07 (1.63 to 2.64)	1.39 (1.08 to 1.78)
Moderate (1 point)					
Myocardial infarction	Normal	43	6.4 (4.5 to 8.7)	1 (reference)	1 (reference)
	Abnormal	54	13.6 (10.3 to 17.5)	2.18 (1.46 to 3.26)	1.84 (1.22 to 2.79)
Stroke	Normal	30	5.7 (4.0 to 8.4)	1 (reference)	1 (reference)
	Abnormal	37	10.1 (7.1 to 13.8)	2.10 (1.30 to 3.40)	1.87 (1.13 to 3.07)
All-cause death	Normal	121	22.7 (18.6 to 27.5)	1 (reference)	1 (reference)
	Abnormal	125	38.6 (32.7 to 45.0)	1.70 (1.33 to 2.19)	1.39 (1.07 to 1.80)
Severe (≥ 2 points)					
Myocardial infarction	Normal	44	10.8 (7.5 to 14.9)	1 (reference)	1 (reference)
	Abnormal	61	14.5 (11.1 to 18.3)	1.92 (1.30 to 2.83)	1.62 (1.08 to 2.42)
Stroke	Normal	47	11.0 (7.6 to 15.1)	1 (reference)	1 (reference)
	Abnormal	31	8.9 (5.9 to 12.5)	0.88 (0.56 to 1.39)	0.82 (0.51 to 1.32)
All-cause death	Normal	138	34.3 (28.6 to 40.8)	1 (reference)	1 (reference)
	Abnormal	182	49.4 (43.6 to 55.6)	1.78 (1.43 to 2.23)	1.56 (1.24 to 1.97)

*Adjusted for sex and age.

Table 4. Hazard ratio of myocardial infarction, stroke, and all-cause death within 10 years following a normal vs. abnormal scan according to diabetes and chronic pulmonary disease status obtained in the 10 years preceding SPECT MPI.

	Scan result	No. of events	Hazard ratio (95% CI)	
			Unadjusted	Adjusted*
With diabetes				
Myocardial infarction	Normal	16	1 (reference)	1 (reference)
	Abnormal	33	2.95 (1.62 to 5.36)	2.43 (1.32 to 4.49)
Stroke	Normal	25	1 (reference)	1 (reference)
	Abnormal	26	1.38 (0.80 to 2.39)	1.26 (0.72 to 2.21)
All-cause death	Normal	53	1 (reference)	1 (reference)
	Abnormal	74	1.88 (1.32 to 2.67)	1.50 (1.05 to 2.16)
Without diabetes				
Myocardial infarction	Normal	141	1 (reference)	1 (reference)
	Abnormal	161	2.44 (1.95 to 3.06)	1.80 (1.42 to 2.28)
Stroke	Normal	125	1 (reference)	1 (reference)
	Abnormal	94	1.35 (1.04 to 1.75)	1.07 (0.82 to 1.41)
All-cause death	Normal	344	1 (reference)	1 (reference)
	Abnormal	364	2.12 (1.83 to 2.46)	1.49 (1.27 to 1.74)
With chronic pulmonary disease				
Myocardial infarction	Normal	37	1 (reference)	1 (reference)
	Abnormal	38	1.89 (1.20 to 2.96)	1.45 (0.90 to 2.33)
Stroke	Normal	28	1 (reference)	1 (reference)
	Abnormal	18	1.16 (0.64 to 2.10)	0.86 (0.46 to 1.60)
All-cause death	Normal	118	1 (reference)	1 (reference)
	Abnormal	115	1.75 (1.35 to 2.26)	1.48 (1.14 to 1.94)
Without chronic pulmonary disease				
Myocardial infarction	Normal	120	1 (reference)	1 (reference)
	Abnormal	156	2.68 (2.11 to 3.40)	1.98 (1.54 to 2.54)
Stroke	Normal	142	1 (reference)	1 (reference)
	Abnormal	102	1.43 (1.11 to 1.84)	1.15 (0.88 to 1.50)
All-cause death	Normal	279	1 (reference)	1 (reference)
	Abnormal	323	2.23 (1.90 to 2.62)	1.49 (1.26 to 1.76)

*Adjusted for sex, age, and comorbidity level.

Appendix

Appendix 1. Charlson Comorbidity Index

Weights	Conditions	**ICD-8 codes**	**ICD-10 codes**
1	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
	Diabetes without end organ damage	249.00; 249.06; 249.07; 249.09; 250.00; 250.06; 250.07; 250.09	E10.0; E10.1; E10.9; E11.0; E11.1; E11.9
2	Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
	Diabetes with end organ damage	249.01-249.05; 249.08; 250.01-250.05; 250.08	E10.2-E10.8, E11.2-E11.8
	Non-metastatic solid tumor	140-194	C00-C75
	Leukaemia	204-207	C91-C95
	Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
3	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
6	Metastatic cancer	195-198; 199	C76-C80
	AIDS	079.83	B21-B24

Appendix 2. Diagnosis codes according to the International Classification of Diseases, 8th (ICD-8) and 10th revision (ICD-10).

	ICD-8	ICD-10
Myocardial infarction	410	I21
Ischemic stroke	433-434	I63-I64
Hemorrhagic stroke	431	I61

Appendix 3. 30-day, 31−365-day, and 1−10-year risk and rate of myocardial infarction, stroke, and all-cause death following a normal vs. abnormal scan.

	Scan result	No. of events	Risk % (95% CI)	Rate (95% CI) per 10,000 patients
30-day				
Myocardial infarction	Normal	2	0.0 (0.0 to 0.1)	47 (12 to 186)
	Abnormal	6	0.2 (0.1 to 0.5)	305 (137 to 679)
Stroke	Normal	3	0.1 (0.0 to 0.2)	70 (23 to 217)
	Abnormal	1	0.0 (0.0 to 0.2)	51 (7 to 361)
All-cause death	Normal	6	0.1 (0.1 to 0.3)	140 (63 to 311)
	Abnormal	4	0.2 (0.1 to 0.5)	203 (76 to 542)
31−365-day				
Myocardial infarction	Normal	25	0.5 (0.3 to 0.7)	55 (37 to 81)
	Abnormal	46	2.0 (1.4 to 2.6)	223 (167 to 298)
Stroke	Normal	30	0.6 (0.4 to 0.8)	66 (46 to 94)
	Abnormal	22	0.9 (0.6 to 1.4)	106 (70 to 161)
All-cause death	Normal	48	1.0 (0.7 to 1.3)	105 (79 to 139)
	Abnormal	41	1.8 (1.3 to 2.4)	196 (145 to 267)
1−10-year				
Myocardial infarction	Normal	130	5.2 (4.3 to 6.4)	62 (52 to 74)
	Abnormal	142	9.8 (8.3 to 11.5)	136 (115 to 160)
Stroke	Normal	137	5.6 (4.6 to 6.8)	66 (56 to 78)
	Abnormal	97	7.3 (5.9 to 9.0)	90 (74 to 110)
All-cause death	Normal	343	15.6 (13.8 to 17.6)	161 (145 to 179)
	Abnormal	393	29.6 (26.9 to 32.4)	355 (321 to 392)

Appendix 4. Risk and hazard ratio of myocardial infarction and stroke during an acute admission within 10 years following a normal vs. abnormal scan.

	Scan result	No. of events	Risk % (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Myocardial infarction	Normal	123	4.4 (3.6 to 5.4)	1 (reference)	1 (reference)
	Abnormal	161	9.9 (8.4 to 11.5)	2.64 (2.09 to 3.34)	1.96 (1.53 to 2.50)
Stroke	Normal	129	4.8 (3.9 to 5.8)	1 (reference)	1 (reference)
	Abnormal	100	6.8 (5.5 to 8.4)	1.52 (1.17 to 1.97)	1.23 (0.94 to 1.61)

*Adjusted for sex, age, and comorbidity level

Appendix 5. 30-day, 31−365-day, and 1−10-year risk of myocardial infarction, stroke, and all-cause death following a normal vs. abnormal scan according to comorbidity level obtained in the 10 years preceding SPECT MPI.

		30-day	31−365-day	1−10-year
Comorbidity level	Scan result	Risk % (95% CI)	Risk % (95% CI)	Risk % (95% CI)
Normal (0 point)				
Myocardial infarction	Normal	−	0.3 (0.1 to 0.5)	4.0 (2.9 to 5.3)
	Abnormal	0.2 (0.0 to 0.7)	1.4 (0.9 to 2.2)	8.0 (6.1 to 10.2)
Stroke	Normal	0.0 (0.0 to 0.3)	0.6 (0.4 to 0.9)	4.5 (3.4 to 5.8)
	Abnormal	−	0.7 (0.3 to 1.3)	6.1 (4.3 to 8.4)
All-cause death	Normal	−	0.4 (0.2 to 0.7)	9.6 (7.8 to 11.8)
	Abnormal	0.1 (0.0 to 0.6)	0.7 (0.3 to 1.4)	18.5 (15.5 to 21.9)
Moderate (1 point)				
Myocardial infarction	Normal	−	0.6 (0.2 to 1.3)	5.7 (3.8 to 8.0)
	Abnormal	−	2.0 (1.0 to 3.5)	11.8 (8.5 to 15.7)
Stroke	Normal	−	0.4 (0.1 to 1.1)	5.3 (3.3 to 8.0)
	Abnormal	−	1.3 (0.6 to 2.5)	9.1 (6.1 to 12.8)
All-cause death	Normal	0.2 (0.1 to 0.8)	1.2 (0.7 to 2.1)	21.6 (17.5 to 26.5)
	Abnormal	−	2.2 (1.3 to 3.8)	37.2 (31.3 to 43.8)
Severe (≥ 2 points)				
Myocardial infarction	Normal	0.1 (0.0 to 0.7)	1.0 (0.5 to 1.9)	10.2 (6.8 to 14.4)
	Abnormal	0.3 (0.1 to 1.2)	2.8 (1.6 to 4.4)	12.1 (8.8 to 16.0)
Stroke	Normal	0.1 (0.0 to 0.7)	0.6 (0.2 to 1.4)	9.6 (6.2 to 14.0)
	Abnormal	−	1.0 (0.4 to 2.1)	8.3 (5.3 to 12.0)
All-cause death	Normal	0.5 (0.2 to 1.3)	3.0 (2.0 to 4.4)	31.9 (26.1 to 38.7)
	Abnormal	0.5 (0.2 to 1.6)	3.7 (2.4 to 5.6)	47.2 (41.2 to 53.7)

Appendix 6. Risk and hazard ratio of myocardial infarction, stroke, and all-cause death within 10 years following a normal vs. abnormal scan according to comorbidity level based on all-available comorbidity information (back to 1977).

Comorbidity level	Scan result	No. of events	Risk % (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Normal (0 points)					
Myocardial infarction	Normal	63	4.0 (3.0 to 5.4)	1 (reference)	1 (reference)
	Abnormal	73	9.2 (7.2 to 11.4)	2.83 (2.02 to 3.97)	2.20 (1.55 to 3.13)
Stroke	Normal	82	4.8 (3.7 to 6.2)	1 (reference)	1 (reference)
	Abnormal	46	6.8 (4.9 to 9.1)	1.33 (0.92 to 1.90)	1.06 (0.73 to 1.54)
All-cause death	Normal	124	9.3 (7.5 to 11.5)	1 (reference)	1 (reference)
	Abnormal	112	17.4 (14.5 to 20.8)	2.00 (1.55 to 2.58)	1.32 (1.01 to 1.72)
Moderate (1 point)					
Myocardial infarction	Normal	46	6.8 (4.9 to 9.3)	1 (reference)	1 (reference)
	Abnormal	56	14.3 (10.8 to 18.3)	2.12 (1.43 to 3.13)	1.74 (1.16 to 2.62)
Stroke	Normal	30	5.5 (3.6 to 8.1)	1 (reference)	1 (reference)
	Abnormal	39	10.4 (7.4 to 14.1)	2.20 (1.37 to 3.54)	1.92 (1.17 to 3.14)
All-cause death	Normal	115	21.2 (17.2 to 25.9)	1 (reference)	1 (reference)
	Abnormal	125	38.2 (32.4 to 44.6)	1.79 (1.39 to 2.30)	1.44 (1.11 to 1.88)
Severe (≥ 2 points)					
Myocardial infarction	Normal	48	9.8 (6.9 to 13.3)	1 (reference)	1 (reference)
	Abnormal	65	13.9 (10.8 to 17.5)	1.98 (1.36 to 2.87)	1.65 (1.12 to 2.44)
Stroke	Normal	58	10.5 (7.4 to 14.3)	1 (reference)	1 (reference)
	Abnormal	35	9.1 (6.3 to 12.6)	0.85 (0.56 to 1.30)	0.80 (0.51 to 1.23)
All-cause death	Normal	158	34.2 (28.8 to 40.2)	1 (reference)	1 (reference)
	Abnormal	201	49.5 (43.9 to 55.4)	1.81 (1.47 to 2.23)	1.58 (1.27 to 1.97)

*Adjusted for sex and age.

Appendix 7. Patients with normal and abnormal scans by sex, age, and comorbidity based on all-available comorbidity information (back to 1977).

	Normal scan (n=5,062)	Abnormal scan (n=2,320)	Total (n=7,382)
Sex			
Female	3,170 (63%)	913 (39%)	4,083 (55%)
Male	1,892 (37%)	1,407 (61%)	3,299 (45%)
Age (years)			
18−49	970 (19%)	269 (12%)	1,239 (17%)
50−59	1,473 (29%)	556 (24%)	2,029 (27%)
60−69	1,512 (30%)	740 (32%)	2,252 (31%)
≥ 70	1,107 (22%)	755 (32%)	1,862 (25%)
Median age (years)	61	65	62
Comorbidity level*			
Normal	3,067 (60%)	1,098 (47%)	4,165 (56%)
Moderate	1,054 (21%)	572 (25%)	1,626 (22%)
Severe	941 (19%)	650 (28%)	1,591 (22%)
Frequent individual comorbidites			
Diabetes	500 (10%)	355 (15%)	855 (12%)
Chronic pulmonary disease	637 (13%)	354 (15%)	991 (13%)

*Levels of comorbidity were based on Charlson Comorbidity Index scores as follows: 0 (normal), 1 (moderate), and ≥ 2 (severe)

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