Journal of the American Heart Association

ORIGINAL RESEARCH

Low Pain Tolerance Is Associated With Coronary Angiography, Coronary Artery Disease, and Mortality: The Tromsø Study

Kristina Fladseth, MD; Haakon Lindekleiv, MD, PhD; Christopher Nielsen, PhD; Andrea Øhrn, MD, PhD; Andreas Kristensen, MD; Jan Mannsverk, MD, PhD; Maja-Lisa Løchen, MD, PhD; Inger Njølstad, MD, PhD; Tom Wilsgaard, PhD; Ellisiv B Mathiesen, MD, PhD; Audun Stubhaug, MD, PhD; Thor Trovik, MD, PhD; Svein Rotevatn, MD, PhD; Signe Forsdahl, MD, PhD; Henrik Schirmer, MD, PhD

BACKGROUND: The initial presentation to coronary angiography and extent of coronary artery disease (CAD) vary greatly among patients, from ischemia with no obstructive CAD to myocardial infarction with 3-vessel disease. Pain tolerance has been suggested as a potential mechanism for the variation in presentation of CAD. We aimed to investigate the association between pain tolerance, coronary angiography, CAD, and death.

METHODS AND RESULTS: We identified 9576 participants in the Tromsø Study (2007–2008) who completed the cold-pressor pain test, and had no prior history of CAD. The median follow-up time was 10.4 years. We applied Cox-regression models with age as time-scale to calculate hazard ratios (HR). More women than men aborted the cold pressor test (39% versus 23%). Participants with low pain tolerance had 19% increased risk of coronary angiography (HR, 1.19 [95% CI, 1.03–1.38]) and 22% increased risk of obstructive CAD (HR, 1.22 [95% CI, 1.01–1.47]) adjusted by age as time-scale and sex. Among women who underwent coronary angiography, low pain tolerance was associated with 54% increased risk of obstructive CAD (HR, 1.54 [95% CI, 1.09–2.18]) compared with high pain tolerance. There was no association between pain tolerance and nonobstructive CAD or clinical presentation to coronary angiography (ie, stable angina, unstable angina, and myocardial infarction). Participants with low pain tolerance had increased risk of mortality after adjustment for CAD and cardiovascular risk factors (HR, 1.40 [95% CI, 1.19–1.64]).

CONCLUSIONS: Low cold pressor pain tolerance is associated with a higher risk of coronary angiography and death.

Key Words: coronary angiography ■ coronary artery disease ■ heart disease risk factors ■ microvascular angina ■ pain measurement

Coronary artery disease (CAD) may initially present as stable angina, unstable angina, or myocardial infarction (MI). The typical presentation of stable angina is exertional chest pain relieved by rest, while acute chest pain is the most common symptom of unstable angina and MI. However, one third of MIs are unrecognized, and sudden coronary death may be the first clinical presentation of CAD.[1–4] On the other hand, half the patients presenting to elective invasive coronary angiography (ICA) and up to 80% of patients presenting to coronary computed tomographic angiography (CCTA) do not have obstructive CAD.[5–8] These discrepancies are challenging because we are likely missing high-risk individuals and exposing low-risk individuals to unnecessary risk of procedural complications at excessive costs to the health care systems.

Symptoms are usually the incentive for seeking medical attention, and determine further testing, diagnosis, and treatment. One hypothesis for the discordance in clinical presentation of CAD is that

Correspondence to: Kristina Fladseth, Cardiovascular Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, 9037 Tromsø, Norway. E-mail: kristina.fladseth@unn.no

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021291

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Low cold pressor pain tolerance was associated with a higher risk of coronary angiography and higher mortality.
- Low cold pressor pain tolerance was not associated with angina with nonobstructive coronary artery disease.

What Are the Clinical Implications?

- Low cold pressor pain tolerance does not explain the discrepancies in the presentation to coronary angiography, from angina with no obstructive coronary artery disease to myocardial infarction with 3-vessel disease.
- Further research is needed to investigate the proposed link between low cold pressor pain tolerance and inflammation.

Nonstandard Abbreviations and Acronyms

FFR	fractional flow reserve
ICA	invasive coronary angiography
IR	incidence rate

differences in pain tolerance affect symptom recognition and help seeking.[9] Smaller studies have demonstrated an association between low pain tolerance, lower anginal threshold, and normal coronary arteries.[10–12] Furthermore, a previous publication from the Tromsø Study found that individuals with unrecognized MI have higher pain tolerance and likely experience fewer symptoms than individuals with recognized MI.[13]

We aimed to investigate the association between pain tolerance and coronary angiography, CAD, and mortality in a general population. We hypothesized that low pain tolerance would be associated with earlier and more coronary angiographies with less obstructive CAD and more often angina than MI. Furthermore, we hypothesized that low pain tolerance would be associated with lower mortality because of earlier diagnosis and/or treatment of CAD.

METHODS

Qualified researchers may apply for access to the data supporting the findings of this study from the Tromsø Study. The syntaxes are available from the corresponding author.

Study Population

The Tromsø Study is a prospective, population-based study, with repeated health surveys of the inhabitants of Tromsø, the largest city in Northern Norway. The sixth survey (Tromsø6), conducted in 2007 to 2008, invited entire and random samples of birth cohorts with a total of 12 984 participants (attendance rate 66%). The participants completed questionnaires and underwent clinical examinations, including experimental pain testing. Further details on recruitment and testing procedures in Tromsø6 have been reported previously.[14] The University Hospital of North Norway is the primary hospital for all inhabitants of Tromsø and was the sole provider of coronary angiography in Northern Norway. From 2005, procedural data from all ICAs performed at the University Hospital of North Norway have been registered in a local quality registry and from May 1, 2013 in a national registry, the NORIC (Norwegian Registry of Invasive Cardiology). By January 1, 2014, the majority of Norwegian hospitals, and from January 1, 2016, all hospitals reported ICA data to NORIC with >99% coverage.[15] In 2013, CCTA was implemented at University Hospital of North Norway as the primary investigation for suspected angina without known CAD, and has been recorded in a registry since then. The national personal identification number allowed for linkage between Tromsø6 and coronary angiography registries on an individual level. Vital status, date of death, and cause of death were obtained from the National Population Register and the Norwegian Cause of Death Registry. The Norwegian Cause of Death Registry is based on the underlying cause of death listed on death certificates, with cardiovascular death defined by ICD (International Classification of Diseases and Related Health Problems), ICD-10: I00–I99, and coronary death defined by ICD-10: I20–I25. More than 80% of deaths in Norway occur in hospitals or other health institutions, thus enabling better determination of cause of death.

Three participants withdrew their consent. We included the 10 486 remaining participants (81%) in Tromsø6 who completed the cold-pressor test (Figure 1). The main reason for not completing the cold pressor test was insufficient test capacity during peak hours (n=1831). Other causes were technical and/or procedural errors, participant refusal or incomprehension, and medical conditions that could interfere with or lead to adverse reactions to the test (n=664). Additionally, we excluded the 722 participants with prior MI or coronary angiography, identified through the MI registry of the Tromsø Study and the coronary angiography registries. This included participants registered with a prior MI or revascularization at their first coronary angiography. Six

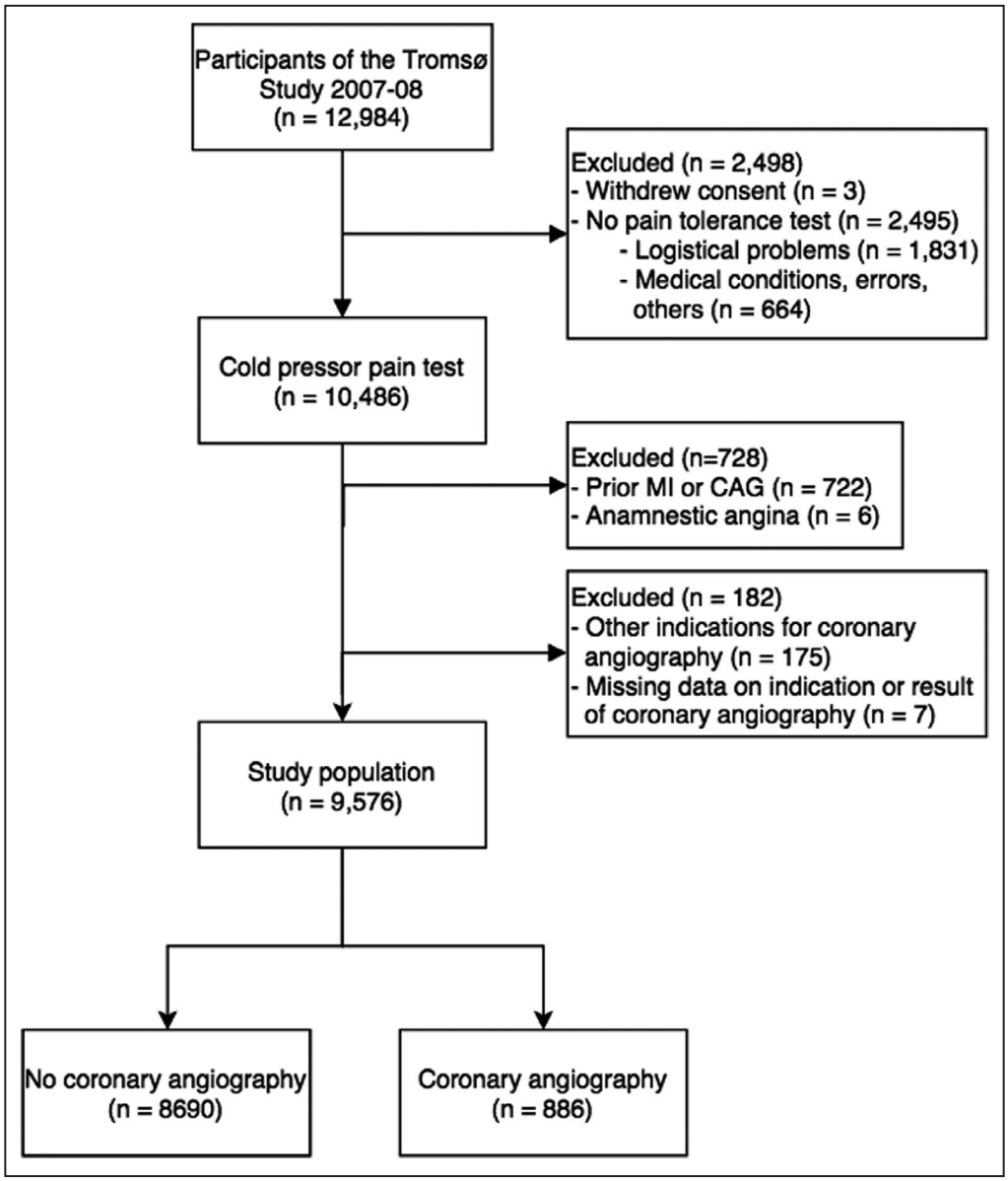


Figure 1. Selection of study participants for The Tromsø Study.
CAG indicates coronary angiography; and MI, myocardial infarction.

participants with self-reported angina and who underwent coronary angiography within 180 days after the baseline examination were excluded. We also excluded 7 participants with missing indication and/or inconclusive result of coronary angiography without a follow-up coronary angiography. Participants referred to coronary angiography as stable angina, unstable angina, and MI were included. Other indications for coronary angiography, such as preoperative assessment before valve surgery, were excluded (n=175). Accordingly, 9576 participants from Tromsø6 were included and followed until coronary angiography, death, or end of follow-up at December 31, 2018. Cause of death was available until December 31, 2017.

Exposures and Covariates

Pain Tolerance and the Cold Pressor Test

The cold pressor test is a well-established experimental pain test, as well as a traditional test of vasospastic angina. The test uses cold, circulating water to induce a deep aching pain by activation of venous nociceptors.[16,17] After a verbal explanation of the test, the participants were asked to place their dominant hand and wrist into a container with 3°C circulating water, and keep it there for as long as possible, up to a maximum of 106 s. The short administration time makes the test well suited for population surveys. Endurance of the cold stimulus until the maximum time was defined as high pain tolerance, whereas aborting the cold

stimulus before the maximum time was defined as low pain tolerance. Further details of the pain testing in Tromsø6 have been reported previously.[18]

Cardiovascular Risk Factors

Data regarding cardiovascular risk factors were collected through clinical examination, blood samples, and self-reported questionnaires. Diabetes was defined as self-reported diabetes, use of antidiabetic drugs and/or hemoglobin A1c ≥48.0 mmol/mol (6.5%); hypertension as self-reported hypertension, mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, and/or the use of antihypertensive drugs; hypercholesterolemia was defined as the use of lipid-lowering drugs, and low-density lipoprotein ≥5.0 mmol/L and/or total cholesterol ≥7.0 mmol/L. Family history of MI was defined as self-reported MI in parents or siblings before the age of 60 years. Body mass index was calculated as measured weight in kilograms divided by the square of measured height in meters. Estimated glomerular filtration rate was calculated according to the CKD-EPI-equation.[19]

Coronary Angiography

The interventional cardiologist or the cardiac radiologist assessed the extent of CAD at the time of the procedure; obstructive CAD was defined as ≥50% diameter stenosis in any epicardial coronary artery.[20] Nonobstructive CAD was defined as 0 to 49% diameter stenosis. When fractional flow reserve (FFR) was measured, obstructive CAD was defined as FFR <0.80. FFR was generally measured with visual diameter stenosis ≈40% to 70%. The extent of obstructive CAD was further described as 1-vessel disease, 2-vessel disease, or 3-vessel disease and/or left main stem disease. CCTA procedures with obstructive CAD or inconclusive results, followed by an ICA in 180 days, were replaced with the results from the ICA. An ICA with obstructive CAD assessed without FFR or revascularization, followed by an ICA with nonobstructive CAD assessed by FFR within 7 days, was replaced with the result of the second ICA. Stable angina, unstable angina, and MI were defined by the interventional cardiologist according to international guidelines at the time of the coronary angiography.

Outcomes

The outcomes were referral to coronary angiography, obstructive CAD (angina or MI with obstructive CAD or coronary death with no preceding coronary angiography), clinical presentation of CAD (stable angina, unstable angina, and MI), extent of CAD (nonobstructive CAD, 1-vessel disease, 2-vessel disease, 3-vessel disease, and/or left main stem disease), and all-cause mortality. Cardiovascular mortality was used as a secondary end point.

Statistical Analysis

Baseline characteristics are reported as counts and percentages or means with SDs. Crude incidence rates (IR) were expressed as number of events per 1000 person-years at risk. The differences in IR were tested using the log-rank test. We used Cox proportional hazard regression models to estimate the hazard ratios (HR) for the association between pain tolerance and coronary angiography, clinical presentation, CAD, and mortality. Because the majority of participants did not abort the cold pressor test, pain tolerance was dichotomized into low pain tolerance and high pain tolerance. Two-way interactions were tested by including cross product terms between the exposure and the adjustment variables in the models. The results were presented stratified if the interaction for sex was significant. There were no other significant interactions. The proportional hazard assumption was tested by Schoenfeld residuals. Because age violated the proportional hazard assumption in most of the analyses, we chose to adjust for age by using age as time-scale. We found the estimates of both methods to be similar. In the mortality analyses, we modeled coronary angiography as a time-varying covariate so that participants contribute with person-time to the no coronary angiography group until the date of the coronary angiography, and afterwards to the angina or MI group.

Covariates had low rates of missing values (0–3%). The rate of missing values for family history of MI is unknown because the variable only included yes or missing response. In the multivariable models, the 9222 participants (96%) with no missing variable for covariates are included.

Statistical analyses were performed in STATA version 16.1 (Stata Corporation, College Station, TX).

Ethics

All participants gave informed written consent, and the Regional Committee for Medical and Health Research Ethics approved the study. The project conducted a data protection impact assessment in agreement with the data protection officials at the University Hospital of North Norway.

RESULTS

We included 9576 participants with no prior history of CAD, of whom 32% aborted the cold pressor test (low pain tolerance) after a median of 46 s and 68% endured the test until the maximum time of 106 s (high pain tolerance). More women than men aborted the

test (39% versus 23%). Baseline characteristics are shown in Table 1. Daily smoking, diabetes, and hypercholesterolemia were more common in participants with low pain tolerance. The median follow-up time was 10.4 years.

Pain Tolerance and Coronary Angiography

Eight hundred eighty six participants were referred to coronary angiography (9.3%), as presumed stable angina (n=468), unstable angina (n=134), or MI (n=284). The IR of coronary angiography was 9.8 (95% CI, 8.7–11.0) and 9.2 (95% CI, 8.5–10.0) per 1000 person-years in participants with low pain tolerance and high pain tolerance, respectively (*P*=0.38). In survival analysis adjusted for sex and age as time-scale, participants with low pain tolerance had a 19% increased risk of coronary angiography (HR, 1.19 [95% CI, 1.03–1.38]) compared with participants with high pain tolerance (Figure 2). There was no interaction by sex for the association between pain tolerance and coronary angiography (*P*=0.80). In a multivariable model predicting coronary angiography, age, sex, hypertension, diabetes, overweight, and family history of premature MI were significant in addition to pain tolerance, which was mildly attenuated to HR 1.17 (95% CI, 1.01–1.34). Other traditional cardiovascular risk factors including smoking did not significantly predict referral to coronary angiography (Table S1).

Pain tolerance was not associated with the presentation of unstable angina versus stable angina (HR, 0.94 [95% CI, 0.52–1.38]), MI, and coronary death versus angina (HR, 1.06 [95% CI, 0.82–1.38]), or acute versus elective referrals (HR, 1.03 [95% CI, 0.80–1.31]).

Pain Tolerance and Degree of CAD

The initial clinical presentation of obstructive CAD was stable angina (n=199), unstable angina (n=66), MI (n=256), and coronary death (n=22). Overall, the IR of obstructive CAD was 5.7 (95% CI, 5.2–6.4) in participants with high pain tolerance and 5.5 (95% CI, 4.7–6.4) in participants with low pain tolerance per 1000 person-years (*P*=0.78) (Table 2). However, adjusting for sex and age as time-scale, participants with low pain tolerance had 22% increased risk of obstructive CAD compared with high pain tolerance (HR, 1.22 [95% CI, 1.01–1.47) (Table 2). The discrepancy in IR and HR is explained by women having less obstructive CAD and more often low pain tolerance. The IR for obstructive CAD per 1000 person-years was 2.7 (95% CI, 2.2–3.4) and 3.4 (95% CI, 2.7–4.3) in women and 8.6 (95% CI, 7.7–9.6) and 9.9 (95% CI, 8.1–12.1) in men with high and low pain tolerance, respectively. There was no interaction by sex for the association between pain tolerance and obstructive CAD in the overall population (*P*=0.64). The association between pain tolerance and obstructive CAD weakened after adjustment for cardiovascular risk factors (HR, 1.16 [95% CI, 0.95–1.40]) (Table 2). All traditional cardiovascular risk factors predicted obstructive CAD (Table S1).

Among participants referred to coronary angiography, women with low pain tolerance had a 54% increased risk of obstructive CAD (HR 1.54 [95% CI, 1.09–2.18]) compared with women with high pain tolerance, after adjustment for cardiovascular risk factors. There was no association in men (Table 2). The interaction term for sex was significant (*P*=0.05). Among women with obstructive CAD, low pain tolerance was associated with nonsignificant higher risk of 3-vessel and/or left main stem disease (HR, 1.99 [95% CI, 0.96–4.13]). Low pain tolerance was not associated with nonobstructive CAD (HR, 1.03 [95% CI, 0.83–1.28]).

Table 1. Baseline Characteristics: The Tromsø Study

Characteristics	High pain tolerance (n=6550)	Low pain tolerance (n=3026)
Age (y)	55±12	56±12
Male sex	53 (3440)	33 (999)
Daily smoker	19 (1259)	25 (760)
Former daily smoker	41 (2665)	40 (1196)
Hypertension	46 (2984)	44 (1322)
Systolic blood pressure (mm Hg)	135±22	132±23
Use of antihypertensive drugs	17 (1097)	20 (596)
Hypercholesterolemia	20 (1297)	23 (702)
Diabetes	6 (420)	9 (280)
Family history of MI	17 (1146)	20 (606)
Body mass index (kg/m^2)	27±4	27±4
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	95±14	95±14

Numbers are mean±SD or percentage (n). Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs, or hemoglobin A1c ≥48 mmol/mol. MI indicates myocardial infarction.

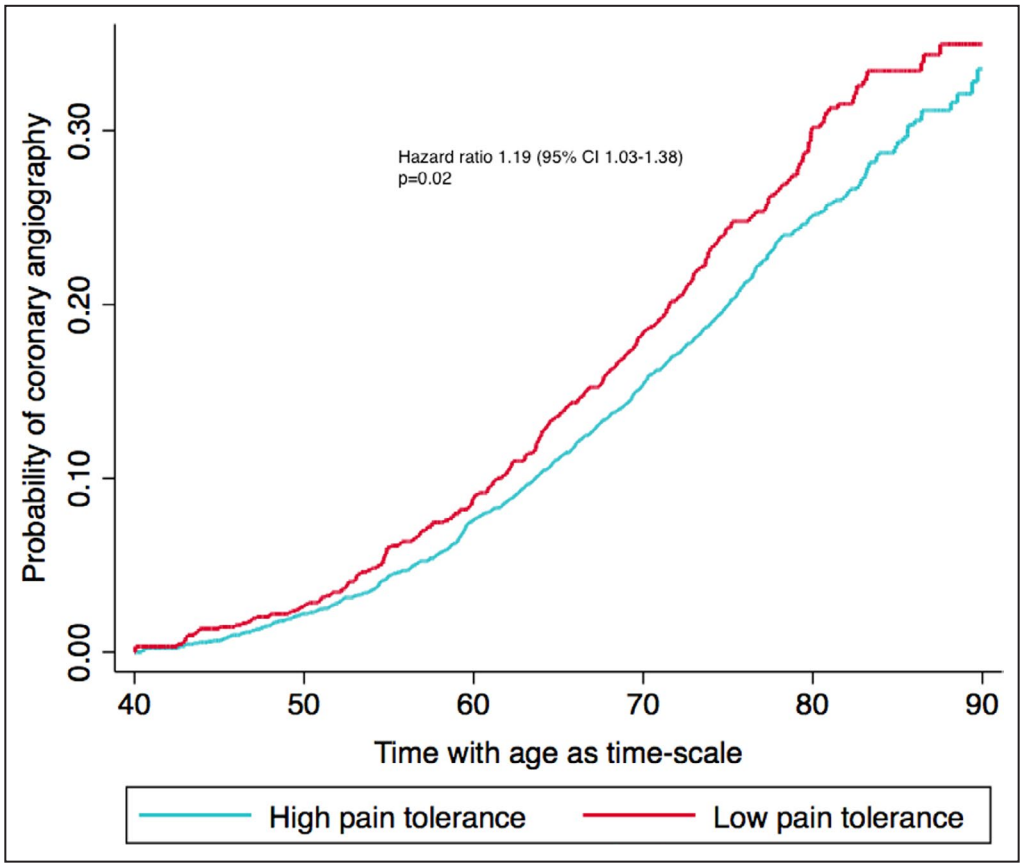


Figure 2. Cumulative incidence function of The Tromsø Study.
Cumulative incidence function for coronary angiography in participants with low pain tolerance and high pain tolerance, adjusted for sex and age as time-scale.

Pain Tolerance and Mortality

A total of 700 participants died (7.3%): 385 men (8.7%) and 315 women (6.1%). The cause of death was available until 2017 for 590 participants, of which 19% was because of cardiovascular disease (69 men and 44 women). Other main causes of death were cancer (51%), injury (8%), respiratory disease (6%), and neurological disease (6%). Overall, the IR of death was 6.4 (95% CI, 5.8–7.0) in participants with high pain tolerance and 8.7 (95% CI, 7.7–9.8) in participants with low pain tolerance (P<0.01). Adjusted for sex and age as time-scale, participants with low pain tolerance had 39% higher risk of death than participants with high pain tolerance (HR, 1.39 [95% CI, 1.19–1.63]) (Figure S1).

Figure 3 show a gradient increase in mortality rate from high pain tolerance to low pain tolerance, and no coronary angiography to MI (P for trend <0.001). In multivariable analyses adjusted for cardiovascular risk factors, participants with no coronary angiography and low pain tolerance had 37% higher risk of death (HR, 1.37 [95% CI, 1.16–1.63]) than participants with no coronary angiography and high pain tolerance. Participants with angina and low pain tolerance had a 2-fold higher risk of death (HR, 2.17 [95% CI, 1.06–4.44]) than participants with angina and high pain tolerance. In participants with MI, the mortality rate was substantially higher, and there we found no association between pain tolerance and mortality.

Table 3 demonstrates the risk of death in univariable and multivariable analyses for low pain tolerance, cardiovascular risk factors, and CAD. Participants with low pain tolerance had increased risk of death after adjustment for CAD and cardiovascular risk factors (HR, 1.40 [95% CI, 1.19–1.64]). The interaction term between pain tolerance and sex was not significant (P=0.73). In sensitivity analyses on cause of death, the results were similar for both cardiovascular death (HR, 1.41 [95% CI, 0.95–2.12]) and other causes of death (HR, 1.39 [95% CI, 1.17–1.66]).

DISCUSSION

We found that low pain tolerance was associated with a 19% higher risk of coronary angiography compared with high pain tolerance. Our results may indicate that individuals with low pain tolerance experience more cardiac symptoms and seek medical help earlier than

Table 2. Incidence Rates and HR for Obstructive Coronary Artery Disease According to Pain Tolerance: The Tromsø Study

Obstructive coronary artery disease*	Events	Person-years	Crude IR per 1000 (95% CI)	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Total population					
High pain tolerance	379	65 936	5.7 (5.2–6.4)	Ref.	Ref.
Low pain tolerance	164	29 896	5.5 (4.7–6.4)	1.22 (1.01–1.47)	1.16 (0.95–1.40)
Men with coronary angiography					
High pain tolerance	282	2475	114 (101–128)	Ref.	Ref.
Low pain tolerance	88	828	106 (86–131)	0.94 (0.74–1.20)	0.89 (0.69–1.15)
Women with coronary angiography					
High pain tolerance	82	1950	42 (34–52)	Ref.	Ref.
Low pain tolerance	69	1298	53 (42–67)	1.46 (1.05–2.01)	1.54 (1.09–2.18)

Model 1 is adjusted for age as time-scale and/or sex; model 2 is adjusted for model 1 + smoking, diabetes, hypertension, hypercholesterolemia, and family history of MI. Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs or hemoglobin A1c ≥48 mmol/mol. HR indicates hazard ratios; IR incidence rate.

*Angina or myocardial infarction with obstructive coronary artery disease on coronary angiography. In the total population, participants with coronary death with no preceding coronary angiography are also included as obstructive coronary artery disease.

individuals with high pain tolerance. This is in line with previous results from the Tromsø Study demonstrating that high pain tolerance was associated with unrecognized MI,[13] as well as 2 studies demonstrating decreased pain sensitivity and more efficient endogenous pain inhibition among individuals with painless MI.[21,22]

Overall, we found that participants with low pain tolerance had a higher risk of obstructive CAD than participants with high pain tolerance adjusted for age as time-scale and sex, but not adjusted for cardiovascular risk factors. Among participants referred to coronary angiography, women with low pain tolerance had a higher risk than women with high pain tolerance for obstructive CAD. These were unexpected findings because we hypothesized that the opposite would be the case. Our findings contradict that patients present with nonobstructive CAD and/or microvascular angina because of lower pain tolerance and increased symptom awareness. Previous studies that compared pain tolerance in angina with and without obstructive CAD had small sample sizes and reported conflicting results with similar cold pressor pain tolerance, higher heat pain tolerance, and lower pain tolerance for ischemic and electrical, as well as cardiac stimuli in angina with no obstructive CAD compared with angina with obstructive CAD.[23–25]

Furthermore, we found that low pain tolerance was associated with increased all-cause mortality in all participants, regardless of referral to coronary angiography. Furthermore, the risk was similarly elevated for cardiovascular death and other death causes. This confutes our hypothesis that individuals with low pain tolerance had a lower risk of dying from CAD, while individuals with high pain tolerance had a higher risk of dying from CAD, even without ever presenting to coronary angiography. We are not aware of any previous study examining associations between pain sensitivity and mortality.

The mechanism by which low pain tolerance might increase the risk of obstructive CAD and all-cause mortality is unclear. We suggest 3 potential mechanisms. First, in our study we observed that individuals with low pain tolerance had a higher burden of traditional cardiovascular risk factors with more daily smoking, hypercholesterolemia, and diabetes. Although we adjusted for these factors in the analysis, and notably pain tolerance was a stronger predictor than many of the traditional risk factors, we still cannot exclude the possibility of residual confounding. Second, low pain tolerance is associated with chronic widespread pain,[18,26] which is further also associated with both increased cardiovascular- and all-cause mortality.[27] Third, another study from the Tromsø Study found higher serum levels of the C-reactive protein in individuals with low pain tolerance.[28] Increased C-reactive protein concentration and inflammation are known risk factors for cardiovascular disease and all-cause mortality, and anti-inflammatory treatment reduces the risk of cardiovascular events.[29–32] Furthermore, the Tromsø Study Fit Futures demonstrated that low cold pressor pain tolerance was associated with lower levels of the omega-3 fatty acids EPA and DHA, lower levels of urokinase plasminogen activator, and higher levels of several inflammatory biomarkers in healthy adolescents aged 15 to 19 years.[33] High levels of EPA are associated with lower risk of cardiovascular disease.[34] Urokinase plasminogen activator is an enzyme used as a thrombolytic agent, and higher levels of urokinase plasminogen activator receptor are associated with cardiovascular mortality.[31] Inflammation as the potential link between low cold pressor pain tolerance and

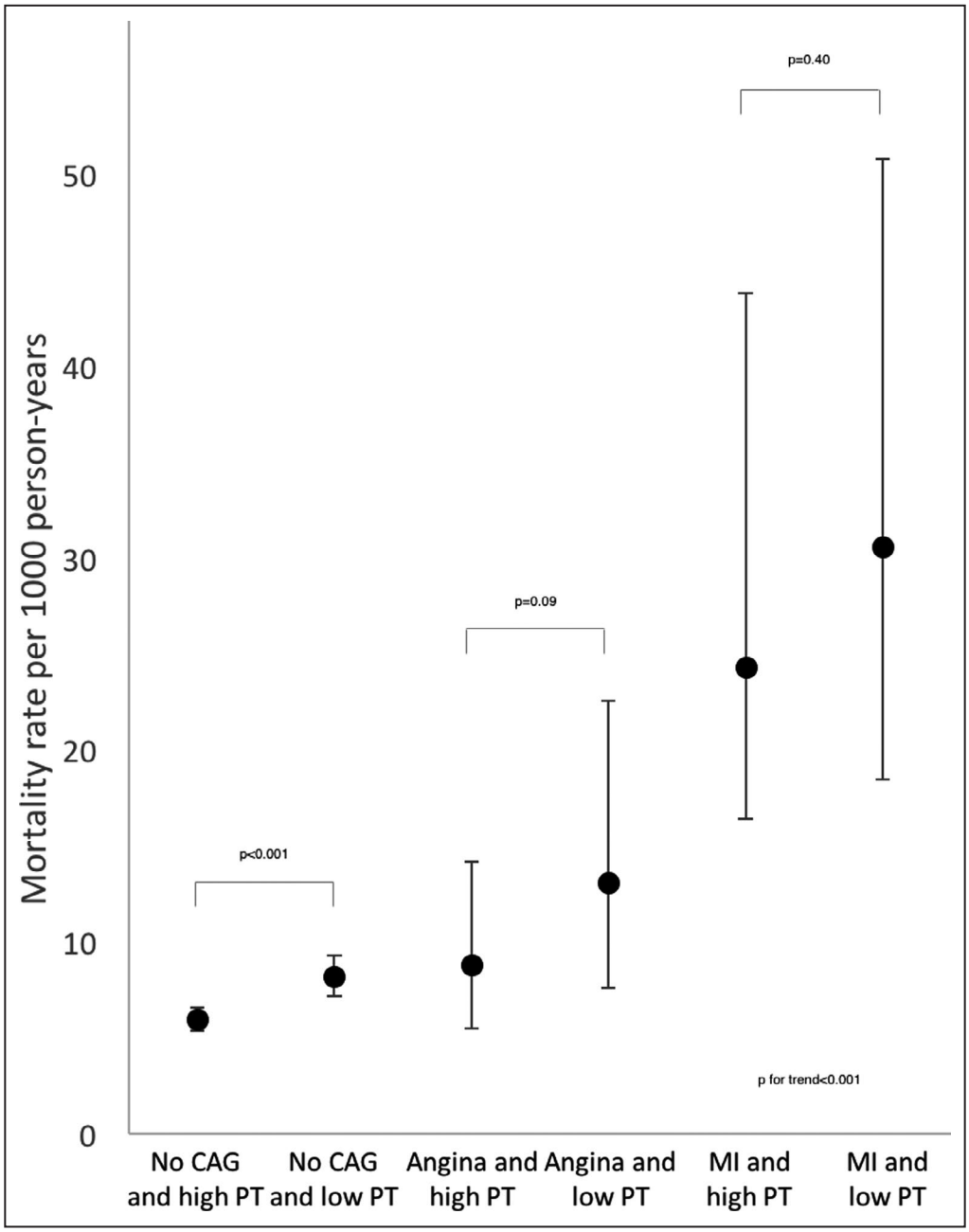


Figure 3. Mortality rate by pain tolerance and coronary artery disease in The Tromsø Study. Forest plot showing the unadjusted mortality rate in participants with high pain tolerance and low pain tolerance, by no coronary angiography, angina, and MI. CAG indicates coronary angiography; MI, myocardial infarction, and PT, pain tolerance. Error bars signify 95% CI.

increased risk of morbidity and mortality is an intriguing hypothesis for further research.

Strengths and Limitations

The strengths of this study include the population-based, prospective cohort design, with cold pressor pain tested in >10 000 individuals, and >10 years of follow-up. Furthermore, the combination of CCTA and ICA data allows for both identification of participants deferred by CCTA and confirmation of all positive findings on CCTA by ICA. We do not know how cold pain tolerance correlates with cardiac ischemic pain tolerance. One small study demonstrated that chest pain was associated with cardiac pain sensitivity, but not with heat pain sensitivity.[23] However, the cold pressor test elicits vascular pain from venous nociceptors, produces vasoconstriction in coronary arteries with endothelial dysfunction and atherosclerosis, and was traditionally used as a noninvasive test of vasospastic angina, and thereby is likely more suitable

Table 3. Univariable and Multivariable Analysis for HR for All-Cause Mortality: The Tromsø Study

	Univariable analysis, HR (95% CI)	Multivariable analysis 1, HR (95% CI)	Multivariable analysis 2, HR (95% CI)
No. of deaths/total no.	663/9222	663/9222	663/9222
Low pain tolerance	1.31 (1.12–1.54)	1.38 (1.18–1.62)	1.40 (1.19–1.64)
Male sex	1.66 (1.42–1.93)	1.74 (1.48–2.04)	1.74 (1.48–2.05)
Hypertension	1.04 (0.87–1.24)	1.05 (0.88–1.26)	1.04 (0.87–1.24)
Hypercholesterolemia	0.94 (0.80–1.12)	0.97 (0.81–1.15)	0.97 (0.81–1.15)
Diabetes	1.50 (1.20–1.87)	1.36 (1.08–1.71)	1.33 (1.06–1.67)
Smoking			
Daily smoker	2.60 (2.10–3.21)	2.46 (1.99–3.05)	2.45 (1.98–3.04)
Former daily smoker	1.50 (1.25–1.81)	1.33 (1.10–1.61)	1.33 (1.10–1.61)
Family history of MI	1.08 (0.88–1.31)	1.10 (0.90–1.34)	1.09 (0.89–1.33)
Body mass index >30 kg/m^2	1.09 (0.90–1.31)	1.12 (0.93–1.36)	1.13 (0.93–1.37)
Estimated glomerular filtration rate <60 mL/min per 1.73 m^2	1.14 (0.84–1.56)	1.08 (0.79–1.47)	1.06 (0.78–1.46)
Coronary angiography			
No coronary angiography	Ref.		Ref.
Angina with obstructive coronary artery disease	1.06 (0.73–1.54)		1.06 (0.73–1.54)
Myocardial infarction	1.69 (1.21–2.36)		1.36 (0.97–1.91)

Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs or hemoglobin A1c ≥48 mmol/mol. Coronary angiography is a time-varying variable. Univariable analysis is adjusted for age as time-scale. In multivariable analysis 1, low pain tolerance is adjusted for age as time-scale, sex, hypertension, hypercholesterolemia, diabetes, smoking, family history of MI, body mass index, and estimated glomerular filtration rate. In multivariable analysis 2, low pain tolerance is adjusted for the variables in multivariable analysis 1 + angina with obstructive coronary artery disease or myocardial infarction with no angiography and nonobstructive coronary artery disease as reference. HR indicates hazard ratios; and MI, myocardial infarction; Ref., reference.

than other peripheral experimental pain measures.[17,35] Furthermore, cold pressor pain tolerance is a hereditary trait and has demonstrated high test–retest reliability.[16,36] Future studies comparing cold pressor test tolerance to cardiac ischemic pain tolerance, and the test–retest reliability over longer periods of time could shed new light on these problems. The conduction of large-scale cardiac pain tolerance testing seems challenging.

Despite the large sample and long follow-up, there were few events of angina, MI, coronary death, and sudden cardiac death. Furthermore, we did not have cause of death for the 110 individuals who died in 2018. This reduces the statistical power of the study, and increases the risk of type II error, particularly in the difference between angina versus MI, and stable angina versus unstable angina, mortality risk ratios among individuals with MI, and cardiovascular mortality. Also, the number of sudden cardiac deaths was too low to conduct meaningful statistical analysis. Sensitivity analyses with pain tolerance run as a continuous or categorized variable demonstrated similar results. National registries ensure near complete follow-up data for the outcomes. However, an individual would be lost to follow-up if the coronary angiography was performed abroad or in another region of Norway before NORIC had full national coverage, and lost to follow-up for death if both emigrated from Norway and no longer registered as a Norwegian citizen. We believe this is unlikely to have affected our results.

CONCLUSIONS

This cohort study indicates that low cold pressor pain tolerance is associated with a higher risk of coronary angiography and all-cause death. Pain tolerance does not seem to explain the different manifestations of CAD, or why more than half of patients presenting to elective coronary angiography do not have obstructive CAD, but further research is needed.

ARTICLE INFORMATION

Received April 12, 2021; accepted September 2, 2021.

Affiliations

Cardiovascular Research Group, Department of Clinical Medicine (K.F., H.S.), Department of Community Medicine (C.N., M.L., I.N., T.W.), Department of Psychology (A.O.) and Department of Clinical Medicine (E.B.M.), UiT The Arctic University of Norway, Tromsø, Norway; Department of Cardiology (K.F., H.L., A.K., J.M., T.T.) and Department of Neurology (E.B.M.), University Hospital of North Norway, Tromsø, Norway; Division of Ageing and Health, Norwegian Institute of Public Health, Oslo, Norway (C.N.); Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway (C.N., A.S.); Institute of Clinical Medicine, University of Oslo, Lørenskog, Norway (A.S., H.S.); Department of Cardiology, Haukeland University Hospital, Bergen, Norway (S.R.); Department of Radiology, University Hospital North

Norway, Tromsø, Norway (S.F.); and Department of Cardiology, Akershus University Hospital, Lørenskog, Norway (H.S.).

Acknowledgments

The authors thank the participants of the Tromsø Study for their contribution and Severin Schirmer for designing the central illustration. Dr. Nielsen's work was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 848099 (PainFACT).

Sources of Funding

This work was supported by an independent PhD grant from Northern Norway Regional Health Authority.

Disclosures

Dr Schirmer reports personal fees from MSD, personal fees from AstraZeneca, personal fees from Sanofi, grants from AstraZeneca, and grants from Novartis outside the submitted work. The remaining authors have no disclosures to report.

Supplementary Material

Table S1
Figure S1

REFERENCES

1. de Torbal A, Boersma E, Kors JA, van Herpen G, Deckers JW, van der Kuip DA, Stricker BH, Hofman A, Witteman JC. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. *Eur Heart J*. 2006;27:729–736. doi: 10.1093/eurheartj/ehi707
2. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris. The Reykjavik Study. *Ann Intern Med*. 1995;122:96–102. doi: 10.7326/0003-4819-122-2-19950 1150-00003
3. Mannsverk J, Wilsgaard T, Mathiesen EB, Lochen ML, Rasmussen K, Thelle DS, Njolstad I, Hopstock LA, Bonaa KH. Trends in modifiable risk factors are associated with declining incidence of hospitalized and non-hospitalized acute coronary heart disease in a population. *Circulation*. 2016;133:74–81. doi: 10.1161/circulationaha.115.016960
4. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012;125:1043–1052. doi: 10.1161/circulatio naha.111.023846
5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895. doi: 10.1056/NEJMo a0907272
6. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870. doi: 10.1161/circulationaha.114.011201
7. Bittencourt MS, Hulten EA, Murthy VL, Cheezum M, Rochitte CE, Di Carli MF, Blankstein R. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. *Circ Cardiovasc Imaging*. 2016;9:4419. doi: 10.1161/circimaging.115.004419
8. Nielsen LH, Bøtker HE, Sørensen HT, Schmidt M, Pedersen L, Sand NP, Jensen JM, Steffensen FH, Tilsted HH, Bøttcher M, et al. Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study. *Eur Heart J*. 2017;38:413–421. doi: 10.1093/eurheartj/ehw548
9. Mehta PK, Bess C, Elias-Smale S, Vaccarino V, Quyyumi A, Pepine CJ, Bairey Merz CN. Gender in cardiovascular medicine: chest pain and coronary artery disease. *Eur Heart J*. 2019;40(47):3819–3826. doi: 10.1093/eurheartj/ehz784
10. Sheps DS, McMahon RP, Light KC, Maixner W, Pepine CJ, Cohen JD, Goldberg AD, Bonsall R, Carney R, Stone PH, et al. Low hot pain threshold predicts shorter time to exercise-induced angina: results from the psychophysiological investigations of myocardial ischemia (PIMI) study. *J Am Coll Cardiol*. 1999;33:1855–1862. doi: 10.1016/s0735-1097(99)00099-6
11. Droste C, Roskamm H. Experimental pain measurement in patients with asymptomatic myocardial ischemia. *J Am Coll Cardiol*. 1983;1:940–945. doi: 10.1016/s0735-1097(83)80214-9
12. Glazier JJ, Chierchia S, Brown MJ, Maseri A. Importance of generalized defective perception of painful stimuli as a cause of silent myocardial ischemia in chronic stable angina pectoris. *Am J Cardiol*. 1986;58:667–672. doi: 10.1016/0002-9149(86)90335-8
13. Ohrn AM, Nielsen CS, Schirmer H, Stubhaug A, Wilsgaard T, Lindekleiv H. Pain tolerance in persons with recognized and unrecognized myocardial infarction: a population-based, cross-sectional study. *J Am Heart Assoc*. 2016;5:e003846. 10.1161/jaha.116.003846
14. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. *Scand J Public Health*. 2013;41:65–80. doi: 10.1177/1403494812469851
15. Hovland S, Seifert R, Rotevatn S. [Annual report 2016]. Norwegian registry of invasive cardiology (NORIC), 2017. Available at: https://www.kvalitetsregistre.no/register/hjerte-og-karsykdommer/norsk-register-invasiv-kardiologi-noric. Accessed April 4, 2021
16. Koenig J, Jarczok MN, Ellis RJ, Bach C, Thayer JF, Hillecke TK. Two-week test-retest stability of the cold pressor task procedure at two different temperatures as a measure of pain threshold and tolerance. *Pain Pract*. 2014;14:126–135. doi: 10.1111/papr.12142
17. Klement W, Arndt JO. The role of nociceptors of cutaneous veins in the mediation of cold pain in man. *J Physiol*. 1992;449:73–83. doi: 10.1113/jphysiol.1992.sp019075
18. Johansen A, Schirmer H, Stubhaug A, Nielsen CS. Persistent postsurgical pain and experimental pain sensitivity in the Tromso study: comorbid pain matters. *Pain*. 2014;155:341–348. doi: 10.1016/j.pain.2013.10.013
19. Levey AS, Stevens LA, Schmid CH, Zhang YI, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006
20. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165. doi: 10.1093/eurheartj/ehy394
21. Granot M, Dagul P, Darawsha W, Aronson D. Pain modulation efficiency delays seeking medical help in patients with acute myocardial infarction. *Pain*. 2015;156:192–198. doi: 10.1016/j.pain.0000000000000020
22. Granot M, Khoury R, Berger G, Krivoy N, Braun E, Aronson D, Azzam ZS. Clinical and experimental pain perception is attenuated in patients with painless myocardial infarction. *Pain*. 2007;133:120–127. doi: 10.1016/j.pain.2007.03.017
23. Cannon RO 3rd, Quyyumi AA, Schenke WH, Fananapazir L, Tucker EE, Gaughan AM, Gracely RH, Cattau EL Jr, Epstein SE. Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. *J Am Coll Cardiol*. 1990;16:1359–1366. doi: 10.1016/0735-1097(90)90377-2
24. Turiel M, Galassi AR, Glazier JJ, Kaski JC, Maseri A. Pain threshold and tolerance in women with syndrome X and women with stable angina pectoris. *Am J Cardiol*. 1987;60:503–507. doi: 10.1016/0002-9149(87)90294-3
25. Lagerqvist B, Sylven C, Waldenstrom A. Lower threshold for adenosine-induced chest pain in patients with angina and normal coronary angiograms. *Br Heart J*. 1992;68:282–285. doi: 10.1136/hrt.68.9.282
26. Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, Knott C, Mulkey F, Rothwell R, Maixner W. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. *J Pain*. 2011;12:61–74. doi: 10.1016/j.jpain.2011.08.006
27. Tesarz J, Eich W, Baumeister D, Kohlmann T, D'Agostino R, Schuster AK. Widespread pain is a risk factor for cardiovascular mortality: results from the Framingham Heart Study. *Eur Heart J*. 2019;40:1609–1617. doi: 10.1093/eurheartj/ehz111
28. Schistad EI, Stubhaug A, Furberg AS, Engdahl BL, Nielsen CS. C-reactive protein and cold-pressor tolerance in the general population: the Tromso Study. *Pain*. 2017;158:1280–1288. doi: 10.1097/j.pain.0000000000000912
29. Lagrand Wim K, Visser Cees A, Hermens Willem T, Niessen Hans WM, Verheugt Freek WA, Wolbink G-J, Hack CE. C-reactive protein

as a cardiovascular risk factor. *Circulation*. 1999;100(1):96–102. doi: 10.1161/01.CIR.100.1.96
30. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497–2505. doi: 10.1056/NEJMoa1912388
31. Frary CE, Blicher MK, Olesen TB, Stidsen JV, Greve SV, Vishram-Nielsen JKK, Rasmussen SL, Olsen MH, Pareek M. Circulating biomarkers for long-term cardiovascular risk stratification in apparently healthy individuals from the MONICA 10 cohort. *Eur J Prev Cardiol*. 2019;27:570–578. doi: 10.1177/2047487319885457
32. Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein and all-cause mortality–the Copenhagen City Heart Study. *Eur Heart J*. 2010;31:1624–1632. doi: 10.1093/eurheartj/ehq103
33. Iordanova Schistad E, Kong XY, Furberg A-S, Bäckryd E, Grimnes G, Emaus N, Rosseland LA, Gordh T, Stubhaug A, Engdahl BO, et al. A population-based study of inflammatory mechanisms and pain sensitivity. *Pain*. 2020;161:338–350. doi: 10.1097/j.pain.0000000000001731
34. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2018;380:11–22. doi: 10.1056/NEJMoa1812792
35. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation*. 1988;77:43–52. doi: 10.1161/01.cir.77.1.43
36. Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain*. 2008;136:21–29. doi: 10.1016/j.pain.2007.06.008

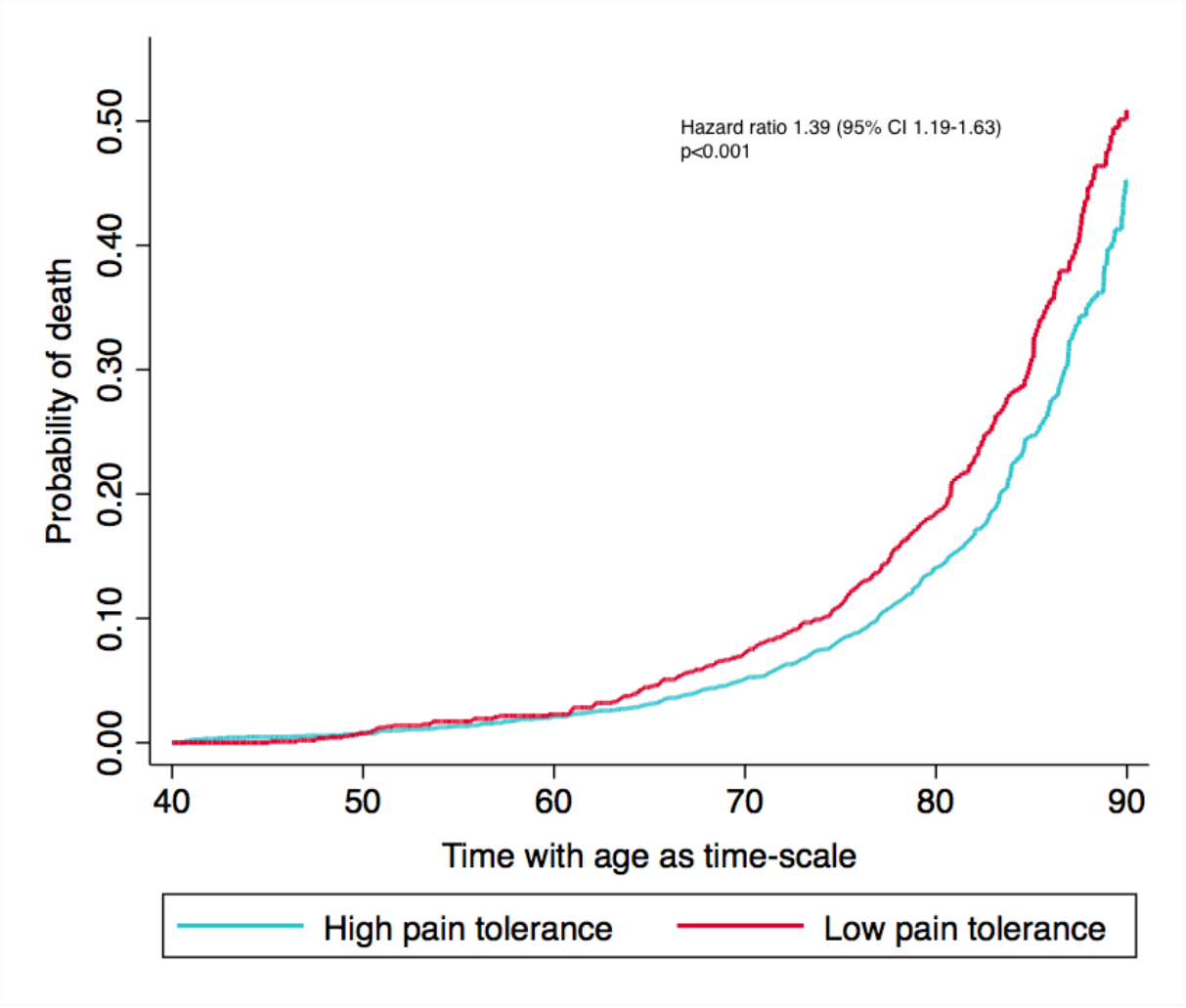
Supplemental Material

Table S1. Risk of Coronary Angiography, Obstructive CAD and Mortality by Cardiovascular Risk Factors and Pain Tolerance, Adjusted for Age as Time-scale and Sex. The Tromsø Study.

	Coronary angiography, HR (95% CI)	Obstructive CAD, HR (95% CI)	All-cause mortality, HR (95% CI)
Daily smoker	1.12 (0.95-1.32)	1.51 (1.24-1.85)	2.12 (1.78-2.51)
Former daily smoker	1.02 (0.89-1.16)	0.91 (0.77-1.08)	0.93 (0.80-1.08)
Hypertension	1.44 (1.25-1.67)	2.00 (1.64-2.43)	1.05 (0.88-1.24)
Hypercholesterolemia	1.17 (1.00-1.36)	1.22 (1.00-1.47)	1.03 (0.87-1.21)
Diabetes	1.46 (1.19-1.80)	1.67 (1.31-2.14)	1.37 (1.11-1.70)
Family history of MI	2.00 (1.73-2.31)	2.15 (1.79-2.59)	1.13 (0.93-1.37)
Body mass index >30 kg/m^2	1.26 (1.08-1.48)	1.27 (1.04-1.55)	1.13 (0.95-1.36)
Estimated glomerular filtration rate < 60mL/min/1.73 m^2	0.73 (0.42-1.28)	1.07 (0.62-1.85)	1.26 (0.94-1.69)
Low pain tolerance	1.19 (1.03-1.38)	1.22 (1.01-1.47)	1.39 (1.19-1.63)

The Tromsø Study 2007-2008. HR indicates hazard ratio; CI, confidence interval. Diabetes is defined as self-reported diabetes, use of anti-diabetic drugs and/or HbA1c≥6.5%; hypertension as self-reported hypertension, use of anti-hypertensive drugs and/or systolic blood pressure≥140 mmHg or diastolic blood pressure ≥90 mmHg; hypercholesterolemia as self-reported, use of lipid-lowering drugs, total cholesterol level≥7 mmol/L and/or low-density lipoprotein ≥5 mmol/L.

Figure S1. Cumulative Incidence Function. The Tromsø Study.



Cumulative incidence function for death in participants with low pain tolerance and high pain tolerance, adjusted for sex and age as time-scale.