Symptoms of angina pectoris increase the probability of disability pension and premature exit from the workforce even in the absence of obstructive coronary artery disease

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Aims
To evaluate probabilities of disability pension (DP) and premature exit from the workforce (PEW) in patients with stable angina symptoms and no obstructive coronary artery disease (CAD) at angiography compared with obstructive CAD and asymptomatic reference individuals.

Methods and results
We followed 4303 patients with no prior cardiovascular disease having a first-time coronary angiography (CAG) in 1998–2009 due to stable angina symptoms and 2772 reference individuals from the Copenhagen City Heart Study, all aged ≤65 years, through registry linkage until 2009 for DP and PEW. Five-year age-adjusted DP-free survival probabilities for reference individuals, patients with angiographically normal coronary arteries, angiographically diffuse non-obstructive CAD, 1 stenotic coronary vessel (1VD), 2VD, and 3VD, respectively, were 0.96, 0.88, 0.84, 0.82, 0.85, and 0.78 in women and 0.98, 0.90, 0.89, 0.89, 0.88, and 0.87 in men. Significant predictors of DP were higher age, angina symptoms, higher body mass index, diabetes, smoking, job status, non-marital status in men, lower income, lower educational level, and co-morbidity. Compared with the reference population, probabilities of DP and PEW were significantly increased in all patients with no gender difference (P < 0.2 for interaction). Thus, in pooled multivariable-adjusted analysis, patients referred to CAG for angina had a three-fold higher probability of DP and ≅50% higher probability of PEW, with little difference between patients with angiographically normal coronary arteries, angiographically diffuse non-obstructive CAD, 1VD, 2VD, and 3VD, the hazard ratios for DP being 2.7, 3.0, 3.3, 3.1, and 3.2 (all P < 0.001) and for PEW being 1.3, 1.4, 1.5, 1.6, and 1.6 (all P < 0.05).

Conclusion
Patients with angina symptoms and angiographically normal coronary arteries, diffuse non-obstructive CAD, or obstructive CAD at angiography have a three-fold increased probability of DP regardless of angiographic findings.

Keywords
Chest pain • Stable angina • Coronary artery disease • Gender • Disability pension • Unemployment

Introduction
Symptoms of stable angina pectoris (SAP) with no obstructive coronary artery disease (CAD) at angiography remain a great challenge for patients and doctors. This seemingly paradoxical condition is not only frequent in clinical practice, as nearly two-thirds of women and one-third of men undergoing first-time coronary angiography (CAG) due to SAP symptoms are found to have no obstructive CAD (defined as 0–49% coronary artery stenosis), but it is also associated with increased risk of adverse cardiovascular events and angina symptoms persisting for years.1,2 We speculated that patients with SAP symptoms and no obstructive CAD at angiography might also

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suffer from a compromised job-related prognosis. The aim of the present study was (i) to evaluate the probability of disability pension (DP) and premature exit from the workforce (PEW) in patients with symptoms of SAP compared with an asymptomatic reference population and how this relates to angiographic disease severity and gender, and (ii) to determine risk factors for DP in these patients.

Methods

In this longitudinal retrospective, registry-based cohort study, we used event-free survival analysis to compare probabilities of DP and PEW in 4415 patients with SAP symptoms, examined with CAG, and 2772 asymptomatic individuals from the Copenhagen City Heart Study (CCHS).

Patient population

The patient population is a subgroup from a large cohort previously described in detail. In brief, all patients having a first-time elective CAG due to symptoms of SAP in Eastern Denmark (representing 43% of the entire Danish population) during 1998–2009 and aged $\geq$ 20 years were included initially ($n = 17,435$) (Figure 1). All patients were referred to CAG by a consultant cardiologist. This decision was based on the patient’s symptoms, risk factors, results of non-invasive tests, and blood samples. Therefore, the angina symptoms were defined by the decision of the cardiologist to refer the patient to CAG with SAP as indication. Patients with prior cardiovascular disease (CVD) [i.e. prior stroke, coronary revascularization, myocardial infarction (MI), or unstable angina] ($n = 6032$) ascertained by central registry linkage were excluded as were patients aged $\geq$ 65 years ($n = 4817$), patients unemployed, retired, receiving benefits or studying at the time of CAG ($n = 2086$), and patients with insufficient data ($n = 157$) (i.e. missing data regarding prior CVD, CAD, or job-related status pre-CAG) or misclassified data ($n = 40$) as explained in detail elsewhere. Patients were treated medically and revascularized according to guidelines.

Asymptomatic reference population

The reference population comprised individuals from the fourth examination of the CCHS taking place in 2001–04. In brief, the CCHS was started in 1976 purporting to study the impact of lifestyle factors on CVD. The population was an age-stratified sample of randomly selected Danish men and women, aged $\geq$ 20 years. The cohort from the first examination was re-invited and supplemented by new participants from younger birth cohorts in 1981, 1991, and 2001. Initially included were 6233 individuals (Figure 1). Individuals with prior CVD ($n = 417$) were excluded as were individuals aged $\geq$ 65 years ($n = 2181$), individuals who at the time of inclusion were unemployed, retired, receiving benefits or studying ($n = 749$), who had angina ($n = 111$) according to

Figure 1  Derivation of the study population.
EXPLANATORY VARIABLES

Outcome data

The primary endpoint was DP before the age of 65 years (the earliest official age of retirement in Denmark in this period). To get a DP in Denmark, you must be deemed permanently unable to work due to physical, psychological, or social reasons. We included a secondary endpoint because we speculated that some patients would withdraw prematurely from the workforce using other available options. Thus, the secondary endpoint was PEW, defined as a composite of unemployment for at least 6 consecutive months, DP, and voluntary early retirement. Early retirement is a publicly co-funded pension scheme which gives you the opportunity to withdraw voluntarily from the workforce from the age of 60 years.

Degree of coronary artery disease

We defined five patient groups based on the degrees of CAD classified by the invasive cardiologist performing the CAG (Figure 1): angiographically normal coronary arteries (no angiographic arteriosclerosis in any coronary artery), angiographically diffuse non-obstructive CAD (angiographic visible arteriosclerosis with <50% stenosis in any epicardial coronary artery); and three groups with successive degrees of obstructive CAD (≥50% stenosis in any epicardial coronary artery): one-vessel disease (1VD), 2VD, and 3VD and/or left main stem stenosis. The reference population served as comparison. The term ‘no obstructive CAD at angiography’ defined angiographically normal coronary arteries and angiographically diffuse non-obstructive CAD as one.

Other variables of interest

Cardiovascular risk factors included age, diabetes, use of lipid-lowering and antihypertensive medication, smoking, body mass index (BMI) (weight/height²), and Canadian Cardiovascular Society Functional classification of angina (CCS class). Socioeconomic factors included civil status, income, job status, and education. Income was defined as last calendar year’s income (prior to CAG/CCHS inclusion). Job status was divided into six categories: top leader (in companies, organizations, or the public sector), self-employed, employee in job that require skills at the highest level (employed/high), at a medium level (employed/medium), and at a basic level (employed/basic), respectively, and other which comprised individuals with little or no personal income, receiving no benefits and not studying (technically, still part of the workforce). Baseline co-morbidity was partly based on a previous study showing that depression, migraine, rheumatic, and lung diseases predict sickness absence from work in angina patients, and partly on a priori assumptions regarding causal web. Thus, baseline co-morbidity was categorized according to the number of the following disease entities causing hospitalization or outpatient contact within 5 years’ pre-inclusion: cancer (ICD-10: C), migraine (ICD-10: G43), depression (ICD-10: F32–F33), chronic obstructive lung disease (COPD) (ICD-10: J44), gastroduodenal ulcer or gastroduodenitis (ICD-10: K25–K27; K29), gastroesophageal reflux (ICD-10: K20–K21; K221), bone, muscle, and connective tissue diseases (ICD-10: M), and kidney diseases (ICD-10: N0–N1). For categorization of the variables, see the tables. There were few missing values for all covariates (0–3%) except the CCS class, which was missing for 14% of the symptomatic population. For further information regarding the data and data sources used in this study see Supplementary material online.

Statistical analysis

Descriptive statistics were used to quantify the distribution of baseline data. The ANOVA or the Kruskal–Wallis rank test were used to test differences in quantitative measures as appropriate, and the χ² test was used to test differences in proportions.

Event-free survival analysis was performed by Cox’s proportional hazards method and aimed at estimating the hazard ratio of outcome in relation to degree of CAD when compared with an asymptomatic reference population. The time frame was defined as time from the CAG or CCHS inclusion till the date of the first event. Individuals were censored at 31 December 2009, time of death, emigration (and thus lack of registry-based follow-up), or at the age of 65 years (or at the date of early retirement in the analyses estimating probability of DP), whichever date occurred first. Event-free survival functions were estimated for different groups with the Kaplan–Meier method. The predictive values of co-morbidity, socioeconomics, and cardiac risk factors in relation to DP were likewise evaluated by means of Cox’s proportional hazards regression. All initial models were gender specific. Only after assessing whether the prognostic value of different CAD degrees was similar in both genders were the analyses repeated on pooled data. Covariates were regarded as confounders of the association between degree of CAD and outcome based on a priori assumptions regarding causal web and if the covariate was associated with outcome after age adjustment with a cut-off for P-value <0.15. Thus, the Cox models were successively adjusted for age, socioeconomics, co-morbidity, and cardiac risk factors. In sensitivity analyses, individuals were excluded if having cardiac co-morbidity, i.e., a previous diagnosis of aortic stenosis, paroxysmal atrial fibrillation, atrial flutter, hypertrophic cardiomyopathy, or perimyocarditis or if such a diagnosis was made within 6 months post-CAG inclusion. Finally, in a multivariable model with all-cause mortality as competing risk, we tested whether differences in mortality could explain the excess probability of outcome associated with the exposure variable. Accurate age adjustment was ensured by splitting each observation in 2-year age groups above the age of 35 before entering in the model as a categorical variable. We treated all other covariates as categorical variables according to the descriptions above with missing values in separate categories to avoid data loss. Since degree of CAD and probability of outcome may reflect gender-specific disease characteristics, we tested for interaction with gender by likelihood ratio tests comparing regression models with and without the interaction terms. Proportionality assumptions were tested and found valid.

All significance testing was two-sided and based on a 5% probability level. All analyses were performed with the Stata 11.1 software (StataCorp, 4905 Lakeway Drive, College Station, TX, USA).

Ethics

This study complies with the Declaration of Helsinki and was approved by the Danish National Board of Health and the Danish Data Protection Agency. Informed consent was given by all participants in the CCHS, which was also approved by the Ethics Committee for the Copenhagen area (KF 100.2039/91).

Results

Baseline characteristics

Baseline characteristics of the study population are shown in Table 1 and Figure 1. Within the symptomatic population, 65% of the women vs. 26% of the men had angiographically normal coronary arteries (P < 0.001).
Reference individuals and patients with angiographically normal coronary arteries were younger than patients with CAD. With the exception of smoking, cardiac risk factors were more prevalent in all five patient groups compared with the reference population and tended to be more prevalent with higher degrees of CAD. A larger proportion of the reference population had never been married and had a low income, but, however, had no co-morbidity, low levels of cardiac co-morbidity, and at the same time 12 years of education. Employment was equally high (≥92%) in reference individuals and patients with the remaining percentages comprising individuals with little or no personal income, receiving no benefits and not studying.

**Probability of disability pension**

Disability pension occurred in 230 women and 294 men during a median follow-up of 5.5 years [inter-quartile range (IQR) 2.5–7.3

### Table 1  Baseline characteristics by study population group

<table>
<thead>
<tr>
<th></th>
<th>Reference n = 2772</th>
<th>Angiographically normal n = 1746</th>
<th>Angiographically diffuse n = 544</th>
<th>1VD n = 901</th>
<th>2VD n = 467</th>
<th>3VD n = 645</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac risk factors, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>48.7 (40–56)</td>
<td>53.9 (48–58)</td>
<td>56.5 (52–60)</td>
<td>56.6 (52–60)</td>
<td>57.6 (52–61)</td>
<td>57.4 (53–61)***</td>
</tr>
<tr>
<td>Male gender</td>
<td>1282 (46)</td>
<td>717 (41)</td>
<td>338 (62)</td>
<td>681 (76)</td>
<td>401 (86)</td>
<td>577 (89)***</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25.2 (4)</td>
<td>26.7 (5)</td>
<td>27.3 (5)</td>
<td>27.2 (4)</td>
<td>27.4 (4)</td>
<td>28.0 (4)***</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 (1)</td>
<td>136 (8)</td>
<td>95 (17)</td>
<td>134 (15)</td>
<td>69 (15)</td>
<td>154 (24)***</td>
</tr>
<tr>
<td>Active smoking</td>
<td>916 (33)</td>
<td>407 (23)</td>
<td>178 (33)</td>
<td>280 (31)</td>
<td>148 (32)</td>
<td>230 (36)***</td>
</tr>
<tr>
<td>CCS class ≥2</td>
<td>916 (33)</td>
<td>407 (23)</td>
<td>178 (33)</td>
<td>280 (31)</td>
<td>148 (32)</td>
<td>230 (36)***</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>33 (1)</td>
<td>748 (43)</td>
<td>365 (67)</td>
<td>600 (67)</td>
<td>339 (73)</td>
<td>492 (76)***</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>192 (7)</td>
<td>609 (35)</td>
<td>291 (53)</td>
<td>426 (47)</td>
<td>228 (49)</td>
<td>344 (53)***</td>
</tr>
<tr>
<td><strong>Socioeconomic factors</strong></td>
<td></td>
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<tr>
<td>Civil status</td>
<td></td>
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</tr>
<tr>
<td>Married/cohabiting</td>
<td>1465 (53)</td>
<td>1238 (71)</td>
<td>367 (67)</td>
<td>665 (74)</td>
<td>333 (71)</td>
<td>480 (74)***</td>
</tr>
<tr>
<td>Divorced/widow</td>
<td>422 (15)</td>
<td>316 (18)</td>
<td>106 (19)</td>
<td>153 (17)</td>
<td>86 (17)</td>
<td>90 (14)</td>
</tr>
<tr>
<td>Never married</td>
<td>885 (32)</td>
<td>192 (11)</td>
<td>71 (13)</td>
<td>83 (9)</td>
<td>48 (10)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>Personal income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18 792€</td>
<td>1233 (45)</td>
<td>667 (38)</td>
<td>198 (36)</td>
<td>295 (33)</td>
<td>176 (38)</td>
<td>231 (36)***</td>
</tr>
<tr>
<td>18 792–35 557€</td>
<td>1300 (47)</td>
<td>814 (47)</td>
<td>262 (48)</td>
<td>480 (53)</td>
<td>233 (50)</td>
<td>332 (50)</td>
</tr>
<tr>
<td>&gt; 35 557€</td>
<td>221 (8)</td>
<td>232 (8)</td>
<td>78 (14)</td>
<td>107 (12)</td>
<td>48 (10)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>Job status</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Top leader</td>
<td>88 (3)</td>
<td>46 (3)</td>
<td>16 (3)</td>
<td>26 (3)</td>
<td>19 (4)</td>
<td>30 (5)***</td>
</tr>
<tr>
<td>Self-employed</td>
<td>195 (7)</td>
<td>139 (8)</td>
<td>56 (10)</td>
<td>114 (13)</td>
<td>66 (14)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>Employed/high</td>
<td>708 (26)</td>
<td>209 (12)</td>
<td>57 (10)</td>
<td>106 (12)</td>
<td>55 (12)</td>
<td>76 (12)</td>
</tr>
<tr>
<td>Employed/medium</td>
<td>548 (20)</td>
<td>311 (18)</td>
<td>82 (15)</td>
<td>117 (13)</td>
<td>76 (16)</td>
<td>68 (11)</td>
</tr>
<tr>
<td>Employed/basic</td>
<td>1093 (39)</td>
<td>905 (52)</td>
<td>299 (55)</td>
<td>483 (54)</td>
<td>219 (47)</td>
<td>340 (53)</td>
</tr>
<tr>
<td>Other</td>
<td>140 (5)</td>
<td>136 (8)</td>
<td>34 (6)</td>
<td>55 (6)</td>
<td>32 (7)</td>
<td>52 (8)</td>
</tr>
<tr>
<td>Education (years of schooling)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 10</td>
<td>248 (9)</td>
<td>320 (18)</td>
<td>121 (22)</td>
<td>166 (18)</td>
<td>85 (18)</td>
<td>130 (20)***</td>
</tr>
<tr>
<td>10–12</td>
<td>486 (18)</td>
<td>246 (14)</td>
<td>59 (11)</td>
<td>110 (12)</td>
<td>49 (10)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>1995 (72)</td>
<td>1125 (64)</td>
<td>3479 (64)</td>
<td>593 (66)</td>
<td>310 (66)</td>
<td>428 (66)</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2300 (83)</td>
<td>1169 (67)</td>
<td>371 (68)</td>
<td>680 (75)</td>
<td>356 (76)</td>
<td>511 (79)***</td>
</tr>
<tr>
<td>1</td>
<td>447 (16)</td>
<td>517 (30)</td>
<td>152 (28)</td>
<td>201 (22)</td>
<td>102 (22)</td>
<td>122 (19)</td>
</tr>
<tr>
<td>≥2</td>
<td>25 (1)</td>
<td>60 (3)</td>
<td>21 (4)</td>
<td>20 (2)</td>
<td>9 (2)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Cardiac co-morbidity</td>
<td>6 (0)</td>
<td>130 (7)</td>
<td>38 (7)</td>
<td>37 (4)</td>
<td>22 (5)</td>
<td>29 (5)***</td>
</tr>
</tbody>
</table>

Co-morbidity reflects the number of the following diseases: migraine, depression, cancer, COPD, peptic ulcer or gastrodudenitis, gastroesophageal reflux, kidney disease, or muscle, bone, or connective tissue disease.

Cardiac co-morbidity, i.e. aortic stenosis, atrial fibrillation/flutter, hypertrophic cardiomyopathy, and perimyocarditis up to 6 months post-CAG/inclusion.

Discrepancies between counts and percentages are due to missing data.

* P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001 for difference between groups.
for ages between 55 and 64. The predictive value of age for DP was partly but not fully caused by higher prevalence of BMI \( > 30 \), diabetes, cardiac and non-cardiac co-morbidity with increasing age (data not shown). Table 2 shows factors predictive of DP. After

<table>
<thead>
<tr>
<th>Study population group</th>
<th>Univariate (age-adjusted) HR (95% CI)</th>
<th>Multivariable-adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events, n</strong></td>
<td><strong>Women</strong></td>
<td><strong>Men</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Women/men</strong></td>
<td><strong>n = 3079</strong></td>
</tr>
</tbody>
</table>

**Cardiac risk factors**

- **BMI (kg/m²)**
  - \(< 25\)
    - (Reference)
  - \(25–30\)
    - 1.5 (1.1–2.1)**
  - \(> 30\)
    - 2.5 (1.8–3.5)***
  - **Diabetes**
    - 2.8 (2.0–4.1)***
  - **Active smoking**
    - 1.4 (1.1–1.9)*
  - **Lipid-lowering medication**
    - 2.3 (1.7–3.0)***
  - **Antihypertensive medication**
    - 1.7 (1.3–2.3)***

**Socioeconomic factors**

- **Civil status**
  - **Married/cohabiting**
    - (Reference)
  - **Divorced/widow**
    - 1.1 (0.8–1.5)
  - **Never married**
    - 0.6 (0.4–1.0)***

- **Personal income**
  - \(< 18 792 €\)
    - (Reference)
  - **18 792–35 557 €**
    - 0.3 (0.3–0.4)***
  - **≥ 35 557 €**
    - 0.2 (0.1–0.4)***

- **Job status**
  - **Top leader**
    - 0.4 (0.1–1.6)
  - **Self-employed**
    - 0.9 (0.5–1.7)
  - **Employed/high**
    - 0.5 (0.3–0.8)*
  - **Employed/medium**
    - 0.7 (0.5–1.0)***
  - **Employed/basic**
    - (Reference)
  - **Other**
    - 4.7 (3.4–6.4)***

- **Education**
  - \(< 10 \text{ years}\)
    - 2.8 (2.1–3.7)***
  - **10–12 \text{ years}\**
    - 1.0 (0.6–1.6)
  - **≥ 12 \text{ years}\**
    - (Reference)

- **Co-morbidity**
  - 0
    - (Reference)
  - 1
    - 2.4 (1.8–3.1)***
  - **≥ 2**
    - 4.7 (2.8–7.8)***

BMI, body mass index; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease and/or left main stem stenosis.

*Stratified by gender and adjusted for age.

\( \ast P < 0.15; \ast\ast P < 0.05; \ast\ast\ast P < 0.01; \ast\ast\ast\ast P < 0.001. \)
multivariable adjustment, higher age, SAP symptoms (patient group), higher BMI, diabetes, active smoking, undefined employment, non-marital status in men, lower income, lower educational level, and the number of co morbidities ($ P < 0.001$ for trend) were significant predictors of DP. Event-free survival during 6.5 years of follow-up is illustrated by the Kaplan–Meier curves in Figure 2. For both genders, overall event-free survival was better in asymptomatic reference individuals than in all five patient groups. The 5-year event-free survival probabilities at an age of 55 years for the reference population, patients with angiographically normal coronary arteries, angiographically diffuse non-obstructive CAD, 1VD, 2VD, and 3VD, respectively, were 0.96, 0.88, 0.84, 0.82, 0.85, and 0.78 in women, and 0.98, 0.90, 0.89, 0.88, and 0.87 in men. Gender-specific age-adjusted Cox models (Table 2) yielded increased probabilities of DP for patients with angiographically normal coronary arteries, patients with angiographically diffuse non-obstructive CAD, and patients with increasing degrees of obstructive CAD (range of HRs 3.1–6.2, all $ P < 0.001$) compared with the reference population. There were no systematic differences in probability of DP for men and women ($ P = 0.61$ for interaction). Thus, pooling the analyses of men and women yielded HRs for angina with angiographically normal coronary arteries of 3.5 [95% confidence interval (CI), 2.7–4.6, $ P < 0.001$], for angiographically diffuse non-obstructive CAD of 4.2 (95% CI 2.9–5.9, $ P < 0.001$), for 1VD of 4.1 (95% CI 3.0–5.6, $ P < 0.001$), for 2VD of 4.2 (95% CI 2.9–6.0, $ P < 0.001$), and for 3VD of 4.9 (95% CI 3.5–6.7, $ P < 0.001$) (age-adjusted model) ($ P < 0.05$ for trend). Adjustment for confounding socioeconomic factors, comorbidity, and cardiac risk factors eliminated the difference between the five patient groups and slightly attenuated the results (Figure 3B), but all five patient groups were still at increased probability of outcome ($ P < 0.001$) compared with the reference population.

### Sensitivity analyses

We tested the robustness of our results by excluding individuals (patients and reference individuals) with cardiac co-morbidity and in a competing risks model with all-cause mortality as competing risk adjusted for age and socioeconomic factors. These sensitivity analyses also showed elevated probabilities of DP (Figure 3C and D) and PEW (results not shown) among all patients compared with the reference population. The probability in patients with no obstructive CAD at angiography was similar to that of patients with 1VD, 2VD, or 3VD.

### Probability of premature exit from the workforce

Premature exit from the workforce occurred in 449 women and 602 men during a median follow-up of 4.8 years (IQR 2.1–7.1 years). For both genders, overall event-free survival was better in asymptomatic reference individuals than in patients (see Supplementary material online, Figure S1). The 5-year event-free survival probabilities age-adjusted to 55 years for the reference population, patients with angiographically normal coronary arteries, angiographically diffuse non-obstructive CAD, 1VD, 2VD, and 3VD, respectively, were 0.86, 0.82, 0.76, 0.77, 0.68, and 0.73 in women and 0.87, 0.82, 0.83, 0.81, 0.78, and 0.77 in men. Gender-specific age-adjusted Cox models (see Supplementary material online, Table S1) showed an increased probability of PEW for patients with angiographically normal coronary arteries, angiographically diffuse non-obstructive CAD, 1VD, 2VD, and 3VD respectively (range of HRs 1.5 and up to 2.8, all $ P < 0.01$), compared with the reference population with no systematic differences in probability for men and women ($ P = 0.23$ for interaction). Thus, pooling the analyses of men and women yielded HRs for angina with angiographically normal coronary arteries of 1.6 (95% CI 1.4–1.9, $ P < 0.001$), for angiographically diffuse non-obstructive CAD of 1.7 (95% CI 1.3–2.2, $ P < 0.001$), for 1VD of 1.8 (95% CI 1.5–2.2, $ P < 0.001$), for 2VD of 2.0 (95% CI 1.6–2.6, $ P < 0.001$), and for 3VD of 2.1 (95% CI 1.7–2.7, $ P < 0.001$) (age-adjusted model) ($ P < 0.01$ for trend) with attenuation after multivariable adjustment to HRs ranging from 1.3–1.6 (all $ P < 0.05$) ($ P < 0.05$ for trend) (see Supplementary material online, Table S1).
Figure 3 Risk of disability pension by study population group in successively adjusted models. (A) Adjusted for age after stratification by gender (non-significant interaction). (B) Further adjusted for education, civil status, job status, income, co-morbidity, body mass index, diabetes, antihypertensive and lipid-lowering medication use, and smoking. (C) Sensitivity analysis: repeating (B) after excluding 262 individuals with a diagnosis of aortic stenosis, paroxysmal atrial fibrillation, atrial flutter, hypertrophic cardiomyopathy, or perimyocarditis up to 6 months post-coronary angiography/inclusion. (D) Sensitivity analysis: repeating (B) as a competing risks model with all-cause mortality as the competing event.
Discussion

This is the first study demonstrating that in patients with symptoms of SAP and no obstructive CAD at angiography, probabilities of DP and PEW are similar to probabilities in patients with obstructive CAD and considerably higher than in an asymptomatic reference population. Differences in age, socioeconomic, co-morbidity, and cardiac risk factors largely explained the differences within the patient group but only partly explained the excess probability in patients compared with the reference population. No differences were found between men and women. The Euro Heart Survey on Angina was initiated partly to establish outcome in terms of important social consequences such as loss of employment, in SAP. However, these data have never been published. Thus, the present study is the first to evaluate the socioeconomic consequences of angina symptoms with no obstructive CAD at angiography since 1986; it is also the first study to do so by making groupwise comparisons of patients by the degree of CAD at angiography with an asymptomatic population as a reference, and the first to evaluate DP as a main outcome and an indicator of the socioeconomic burden of disease both to the individual and to society.

Angina despite no obstructive coronary artery disease at angiography

Why some patients have SAP symptoms in the absence of obstructive CAD has several possible explanations. Some of these patients probably have rhythm disturbances, aortic stenosis, or hypertrophic cardiomyopathy. However, excluding patients later diagnosed with these conditions did not significantly alter the results. Some patients surely have SAP symptoms due to non-cardiac causes like COPD, musculoskeletal disorders, gastric peptic diseases, personality or psychiatric disorders. Previously, angina symptoms with no obstructive CAD at angiography have often been ascribed to psychological problems such as anxiety and depression and indeed these are shown to be correlated. Psychological disorders may be part of the aetiology of ischaemic heart disease and symptoms thereof, but may in fact also be normal and expected reactions to unexplained and poorly managed angina. More research is needed to clarify the causality between angina symptoms with no obstructive CAD at angiography, psychological morbidity, and socioeconomic consequences. In the present study, adjustment for confounding non-cardiac causes of SAP symptoms attenuated but not nearly eliminated the increased probabilities of outcomes in patients vs. reference individuals. Another possibility is that some patients with angina and no obstructive CAD at angiography have coronary microvessel dysfunction causing characteristic symptoms of cardiac ischaemia. Several studies have established high prevalence of abnormal coronary flow and abnormal metabolic responses to stress consistent with myocardial ischaemia in patients with anginal symptoms and no obstructive CAD at angiography.

Job status in ischaemic heart disease

In two studies from the 1980s, it was shown that 14–19% of patients with angina symptoms and < 30% coronary artery stenosis at angiography had stopped working for cardiac reasons at 4–6 years post-CAG, compared with 24% of patients with 25–75% coronary artery stenosis. These rates correspond well with those reported in the present study with 18% of patients with angiographically normal coronary arteries and 18–25% of patients angiographically diffuse non-obstructive CAD having prematurely left the workforce at 5 years of follow-up. In the RITA trial, 23% of 218 men with SAP were not working due to unemployment, retirement, or inability to work 2 years after CABG or coronary angioplasty. This represents a higher rate in patients with obstructive CAD than the 20–32% after 5 years presented in the present study and may be due to more severe CAD in the RITA trial patients of whom 75% had severe angina (class > 3) at randomization compared with only 17% in our study. As for the reference population, 6% of the entire Danish population was assigned DP in 2012 between the ages of 50 and 59 years. This number corresponds well to those reported in the present study with 2–4% of reference individuals assigned DP after 5 years of follow-up. The social security systems, employment legislation, and unemployment rates presumably influence societal changes in job status and the effect may vary by year and country. Therefore, one should be cautious when comparing absolute event rates for different countries or time periods. However, one would expect the effect of social security, employment legislation, and unemployment rates on changes in job status to be equal in patients with angina symptoms and in asymptomatic individuals (after multivariable adjustment). Thus, the main finding from the present study that angina symptoms increase the probability of DP and PEW irrespective of the presence of CAD at CAG should be applicable to other European countries.

Predictors of disability pension

Factors significantly predicting DP were higher age, SAP symptoms, higher BMI, diabetes, smoking, undefined employment, lower income, lower educational level, non-marital status in men, and the number of co-morbidities. The predictive value of age for DP was partly but not fully caused by a higher prevalence of BMI > 30, diabetes, cardiac and non-cardiac co-morbidity with increasing age. The asymptomatic reference population was 5–9 years younger than the patient groups, and, therefore, to ensure the validity of the results, all analyses were carefully age-adjusted. In a previous study, SAP predicted sickness absence in the general population. This was largely ascribed to co-morbidities like depression, migraine, rheumatic and lung diseases. Studies of non-return to work after revascularization in SAP and after angiography or revascu larization in MI patients have identified the following predictors: higher age, manual labour, non-marital status, shorter education, extra-cardiac vascular disease, poorer psychological status, lower level job classification, as well as depression and persistent angina. The present study extends these findings to patients with angina symptoms with and without obstructive CAD. Interestingly, persistency of angina symptoms has previously been identified in more than half of patients with no obstructive CAD at angiography. Altogether, in patients with symptoms of SAP and no obstructive CAD at angiography, the major excess probability of not working may reflect the risk associated with having unexplained and poorly managed persistent angina.

Strengths and limitations

Our study reflects practice in a nationwide sample of patients. The large sample size of 4303 symptomatic patients and 2772 asymptomatic reference individuals, the wide range of ages, the 524 primary
events and 1051 secondary events during >5 years of follow-up and the complete follow-up (only 157 patients were excluded due to insufficient data) are important strengths of this study.

The study has some limitations. Probably, the symptomatic population included both appropriate and inappropriate referrals; still the referral pattern would be applicable to other populations referred to angiography. The patient groups were defined on the basis of the angiography descriptions by several invasive cardiologists performing the CAGs, and as a result, there may be some overlap between angiographically normal coronary arteries and angiographically diffuse non-obstructive CAD. However, in the present analysis, such bias is of less importance, as the prognosis is the same for both groups. All information was obtained from nationwide registries and the database containing information on the CAGs, all in which data entry is performed continuously. Thus, the retrospective design and the use of data in the present study are not likely to have introduced any bias. Probably, the included patients’ angina symptoms were due to a variety of causes. No baseline data on the psychological status of the patients was available. Instead, we used information on hospitalization and outpatient contacts due to depression within 5 years pre-CAG as a marker of psychological co-morbidity in the study population. Adjustment for eventual confounding cardiac and non-cardiac causes of angina symptoms and co-morbidity had little effect on the results. However, the data do not contain individual reasons for DP and do not provide insights into the mechanisms of angina with no obstructive CAD at angiography nor into the clinical outcomes of patients with and without DP stratified by CAG results.

Conclusions

In conclusion, our study shows that among patients with symptoms of SAP, patients with angiographically normal coronary arteries and angiographically diffuse non-obstructive CAD have the same increased probability of future DP and PEW as patients with obstructive CAD, even after multiple adjustments. No gender differences were found. Thus, contrary to common perception, excluding obstructive CAD by CAG in patients with SAP symptoms does not ensure a favourable job-related prognosis, and further risk stratification and treatment strategies targeting this group are warranted.

Clinical implications

The results from the present study highlight the importance of understanding the mechanisms of angina symptoms despite no obstructive CAD at angiography. This condition involves a heterogeneous group of patients having angina symptoms for very different reasons ranging from somatic, non-cardiac co-morbidity, and personality and psychiatric disorders to cardiac co-morbidity. Importantly, there is an increasing amount of evidence supporting the hypothesis that a considerable part of these patients have angina caused by coronary microvascular dysfunction, which is not diagnosed by routine CAG. Future research should aim at identifying the multiple underlying causes in order to improve treatment and the job-related prognosis in these patients.

Supplementary material

Supplementary material is available at European Heart Journal online.

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