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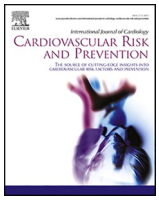

Association of overweight and obesity with coronary risk factors and the presence of multivessel disease in patients with obstructive coronary artery disease – A nationwide registry study

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ABSTRACT

Background: The growing prevalence of obesity is expected to increase the burden of coronary artery disease. This study examined the prevalence of overweight and obesity in patients with a first-time diagnosis of obstructive coronary artery disease in a contemporary population. The association of body-mass-index (BMI) with age, traditional risk factors, and the presence of multivessel disease were explored.

Methods and results: Using the Danish Nationwide registries, we identified 49,733 patients with a first-time diagnosis of obstructive coronary artery disease in the period 2012–2018. We investigated the association between BMI and coronary risk factors by multivariate logistic regression. Mean age was 65.8 ± 11.8 years, mean BMI was 27.5 kg/m^2 ± 7.2, and 73.2 % were men. 66.3 % had a BMI ≥25 kg/m^2 and 1.3 % were underweight. The prevalence of patients with BMI ≥25 kg/m^2 decreased with increasing age and was 69 % in patients <50 year vs. 46.2 % in patients ≥80 years ($p < 0.001$). In all age groups, higher odds of BMI ≥25 kg/m^2 were observed in males, former smokers, and patients with hypertension. In multivariate logistic regression, BMI ≥25 kg/m^2 was not associated with presence of multivessel disease ($p = 0.74$).

Conclusion: In this large, nationwide study, 66.3 % of patients with first time diagnosis of obstructive coronary disease had BMI ≥25 kg/m^2. Young patients had higher BMI and were more likely to be current smokers. Overweight or obesity was independently associated with the presence of diabetes and hypertension. BMI ≥25 kg/m^2 was not independently associated with the presence of multivessel disease.

1. Introduction

Coronary artery disease is one of the main causes of mortality and morbidity worldwide [1,2]. However, mortality caused by coronary artery disease has decreased over the recent decades partly due to improved prevention and revascularization techniques [3,4]. Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in combination with prophylactic therapy are the cornerstones of treatment for coronary artery disease [5].

Patients with coronary artery disease often have several coronary risk factors, such as hypertension, dyslipidemia, overweight or obesity, and decreased insulin sensitivity [6,7]. Clustering of these risk factors, the 'metabolic syndrome' [8,9], increases the risk of diabetes mellitus and coronary artery disease [10,11]. Obesity is fundamental in the development of the metabolic syndrome due to its role as a contributing factor in the development of several coronary risk factors, and is probably an independent risk factor for coronary artery disease [10,12,13].

The growing prevalence of obesity is assumed to increase the burden of coronary artery disease and related mortality [14,15]. However, studies have demonstrated a protective association of obesity on prognosis (i.e. the obesity paradox) after coronary revascularization [16–19]. Further investigation is needed to explore the association between coronary risk factors, body max index (BMI), and the severity of coronary artery disease. Large studies are needed to study the effect of patient age on this association due to the slow progression of coronary artery disease.

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In this nation-wide, contemporary, observational study of patients with invasively diagnosed obstructive coronary artery disease, the main objective of the study was to examine 1) the current prevalence of overweight and obesity, 2) the association between BMI and coronary risk factors in relation to age, and 3) the association between BMI and the presence of multivessel disease. We hypothesized that BMI is associated with coronary risk factors, that these associations vary by age, and that BMI is associated with the presence of multivessel disease.

2. Methods

2.1. Study population

We included patients aged 18–100 years who underwent invasive coronary angiography (ICA) in Denmark and received a first-time diagnosis of obstructive coronary artery disease between January 1st, 2012 and January 1st, 2018. Patients with a history of ischemic heart disease (defined by the International Classification of Disease (ICD-10) codes I20–I25) were excluded. Due to notable missing data on important variables past 2018, we chose to focus on the years 2012–2018 to ensure consistency in our analysis. The population was divided into age groups (<50, 50–59, 60–69, 70–79, and ≥80 years) and BMI-categories. Underweight, normal weight, overweight and obesity class I and class II were defined as BMI <18.5, 18.5 to 24.9, 25 to 29.9, >30 to 34.9 and > 35 kg/m^2, respectively [20]. Referral types for ICA was divided into acute (predominantly ST-segment elevation myocardial infarction and high-risk non-ST-segment elevation myocardial infarction (NSTEMI)), subacute (NSTEMI and unstable angina pectoris), or elective (chronic coronary syndrome). Multivessel disease was defined as obstructive disease in two or more major coronary territories (left anterior descending, left circumflex, or right coronary artery).

2.2. Data sources

The health care system in Denmark is free and government funded. All permanent residents are assigned a unique personal ten-digit identifier at birth or immigration. In this study, all data were obtained from Danish nationwide registries. The unique identifier makes it possible to cross-link data from registries on an individual level [21].

Data on vital status, gender, year of birth, and year of death were obtained from The Danish Civil Registry [22]. Data on smoking, BMI, severity of coronary artery disease (obstructive disease involving one, two, or three main coronary territories), referral types, and cardiac invasive procedures (ICA, PCI, and CABG) were obtained from The Danish Heart Registry [23]. Data on hospital contacts such as diagnoses and comorbidities were obtained from The Danish National Patient Registry [24]. Data on dispensing date and type of drug of redeemed medical prescriptions were obtained from The Danish National Prescription Registry. Medications were registered according to the Anatomical Therapeutic Chemical classification (ATC) [25].

2.3. Comorbidities and medication

Comorbidities were identified using ICD-10 codes registered up to ten years prior to the first ICA with a diagnosis of obstructive coronary artery disease (see supplementary Table 1). Medical prescriptions filled up to six months prior to enrollment were considered current medications. Presence of diabetes mellitus and hypertension were defined as the use of antidiabetic medication and the use of a minimum of two types of antihypertensives, respectively (see supplementary Table 1 for further details) [26].

2.4. Statistical analysis Categorial variables are presented as numbers and percentages with 95 % confidence intervals (CI). Continuous variables are presented as means and standard deviations (SD). To investigate the association between BMI, coronary risk factors, and severity of coronary artery disease, we performed multivariate logistic regression to compute odds ratios (OR).

We plotted the prevalence of coronary risk factors, BMI, and multivessel disease across age groups. To test the interaction of age on the association between BMI and coronary risk factors, we used logistic regression with presence of a given coronary risk factor as the dependent variable and age and BMI as covariates. Results were presented as ORs with 95 % CIs. Missing data were assumed to be missing at random and all analyses were performed as complete case analyses. A two-sided p-value below 0.05 was considered significant. Statistical analyses were conducted using Rstudio (version 4.2.1) [27].

3. Results

A total of 145,809 patients underwent ICA from January 1st, 2012, to January 1st, 2018. Of these, 48,213 patients were excluded due to a history of coronary artery disease. Furthermore, 47,863 patients were excluded due to absence of obstructive coronary artery disease. We ultimately included 49,733 patients with a first-time invasive diagnosis of obstructive coronary artery disease (Fig. 1).

The mean age was 65.8 ± 11.8 years, mean BMI was 27.5 kg/m^2 ± 7.2, and 73.2 % were men. 32.3 % were normal weight, 1.3 % were underweight, and 66.3 % had a BMI ≥25 kg/m^2 (Table 1). The prevalence of coronary risk factors varied across BMI-categories regarding age, diabetes mellitus, hypertension, any smoking status, and the total number of risk factors. Patients with a higher BMI were characterized by lower age, predominance of male sex and a higher number of former smokers (all tested individually and significant at $p < 0.001$). Conversely, we found that underweight patients were characterized by higher age, female predominance, and the highest prevalence of current smokers. Being a current smoker was more commonly observed in the lower BMI-categories. More former smokers were observed in the overweight BMI-categories compared to the normal and underweight categories. More patients had never smoked in the overweight BMI-categories (16.4 %) compared to patients with a BMI <25 (8.4 %). We observed a higher prevalence of diabetes mellitus, statin-use, and hypertension and more patients with at least 3 risk factors among patients in the higher BMI-categories. Also, we observed a decrease in the prevalence of diabetes, hypertension and smoking throughout the study period (13.5 %–12.8 % ($p = 0.044$), 36.3 %–26.4 % ($p < 0.001$) and 66.5 %–56.9 % ($p < 0.001$), respectively. However, there was an increase in BMI from 27.0 kg/m^2 to 27.5 kg/m^2 throughout the study period ($p < 0.001$) (see Supplementary Figure 1).

When stratifying for age groups, the proportion of patients being overweight decreased with age, 69 %, 67.1 %, 65.5 %, 58.6 %, 46.2 % for patients aged <50, 50–59, 60–69, 70–79, and ≥80, respectively ($p < 0.001$). The prevalence of coronary risk factors resembled the overall results in the non-stratified cohort (Fig. 2). Across all age groups, there was a higher prevalence of diabetes and hypertension in patients with BMI ≥25 kg/m^2. For all age groups except ≥80 years, underweight patients had a higher prevalence of current smoking. Within the higher BMI-categories, a lower prevalence of current smoking and a higher prevalence of former smoking were observed. In general, we observed a higher prevalence of current smokers within the lower age groups.

Odds ratios for the association between risk factors and BMI ≥25 kg/m^2 stratified by age are shown in Fig. 3. In all age-groups, we observed higher odds of BMI ≥25 kg/m^2 in male patients, former smokers, and patients with hypertension. In the age-group <50 years, we observed no significant differences in the odds for having a BMI ≥25 kg/m^2 among patients with diabetes or current smoking. We found significant interactions of age on the association between BMI and risk factors for former smoking, hypertension, and diabetes ($p = 0.007$, $p = 0.02$, $p = 0.02$, respectively). When stratifying for referral types, all three groups showed the same distribution of risk factors between BMI-categories.

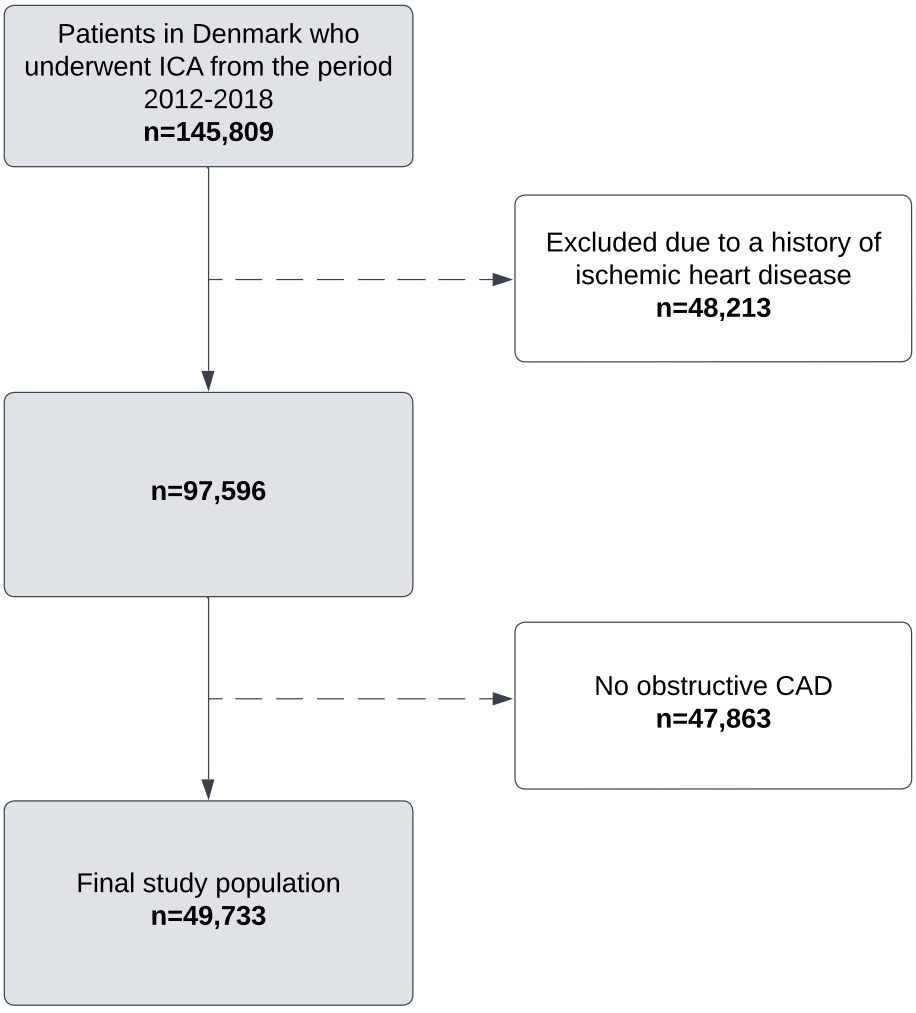

Fig. 1. The flowchart of exclusion and inclusion criteria for the study population. ICA = Invasive coronary angiography, CAD = coronary artery disease.

Table 1
Baseline characteristics stratified by BMI.

	Total[a]	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	>35	*p*-value[b]
No. (n)	49,733	632	15,183	19,713	8,185	2,871	
Age, years (SD)	65.8 (11.8)	70.5 (12.0)	67.9 (12.0)	65.6 (11.4)	63.5 (11.3)	61.2 (11.4)	<0.001
Male, n (%)	3,6397 (73.2)	202 (32.0)	10,124 (67.7)	15,538 (78.8)	6,362 (76.5)	1,957 (68.2)	<0.001
Smoking status[c], n (%)							<0.001
Current	14,391 (32.6)	303 (53.5)	4,950 (36.6)	5,378 (30.2)	2,239 (29.9)	808 (30.7)	
Former	16,782 (38.0)	140 (24.7)	4,615 (33.8)	7,165 (40.2)	3,088 (41.3)	1,051 (40.0)	
Never	12,989 (29.4)	123 (21.7)	4,071 (29.9)	5,267 (29.6)	2,151 (28.8)	771 (29.3)	
Diabetes mellitus, n (%)	6,819 (13.7)	50 (7.9)	1,362 (9.0)	2,535 (12.9)	1,655 (20.1)	800 (27.9)	<0.001
Hypertension, n (%)	16,809 (33.8)	169 (26.7)	4,248 (28.0)	6,694 (34.0)	3,362 (41.1)	1,376 (47.9)	<0.001
Statin users, n (%)	17,048 (34.3)	172 (27.2)	4,747 (31.3)	6,896 (35.0)	3,154 (38.5)	1,129 (39.3)	<0.001
Referral type, n (%)							<0.001
Acute	17,423 (35.0)	231 (36.6)	5,641 (37.2)	6,863 (34.8)	2,544 (31.1)	909 (31.7)	
Subacute	14,662 (29.5)	205 (32.4)	4,351 (28.7)	5,636 (28.6)	2,426 (29.6)	912 (31.8)	
Elective	17,611 (35.4)	195 (30.9)	5,184 (34.1)	7,200 (36.5)	3,208 (39.2)	1,047 (36.5)	
≥3 risk factors, n (%)	16,365 (32.9)	191 (30.2)	4,268 (28.1)	6,455 (32.7)	3,270 (40.0)	1,321 (46.0)	<0.001
Multivessel disease, n (%)	23,367 (47.0)	291 (46.0)	7,090 (46.7)	9,350 (47.4)	3,902 (47.7)	1,260 (43.9)	0.0141
Revascularization: n (%)							
PCI	35,269 (70.9)	406 (64.2)	10,595 (69.8)	14,080 (71.4)	5,859 (71.6)	2,075 (72.3)	
CABG	9,548 (19.2)	62 (9.8)	2,864 (18.9)	4,028 (20.4)	1,649 (20.1)	470 (16.4)	<0.001

[a] Missing BMI for 3,149 patients.
[b] P-value for trends.
[c] Missing smoking status for 5,571 patients. BMI: body mass index. PCI: Percutaneous coronary intervention. CABG: Coronary artery bypass grafting.

3.1. Multivessel disease

As reported in Table 1 and 53 % had one-vessel disease and 47 % had multivessel disease in the total cohort. We observed a slightly higher proportion of patients with multivessel disease in patients with BMI 25–29.9 and 30–34.9, and a slightly lower proportion in the category

Fig. 2. The prevalence of diabetes, hypertension and the proportion of current smokers and formers smokers in the BMI-categories, stratified in age groups. X-axis depicts BMI-categories and Y-axis depicts the prevalence in percentage.

≥35 kg/m^2 (Table 1). In multivariate logistic regression, BMI ≥25 kg/m^2 was associated with higher odds of multivessel disease after adjusting for age and sex (odds ratio 1.08, 95 % [CI 1.03; 1.12], $p < 0.001$). After further adjustment for diabetes, hypertension, and smoking, the association disappeared. Diabetes, hypertension, and smoking status remained associated with multivessel disease in the multivariate model ($p < 0.001$) (Table 2).

4. Discussion

In this nationwide cross-sectional registry study, we included 49,733 patients with a first-time invasive diagnosis of obstructive coronary artery disease. We found that 66.3 % of patients had a BMI ≥25 kg/m^2 and that the prevalence of overweight was greatest in patients <50 years. There was a higher prevalence of diabetes and hypertension in patients with BMI ≥25 kg/m^2 and a higher prevalence of current smoking in patients with BMI <25. There was no association between BMI ≥25 kg/m^2 and presence of multivessel disease in multivariate analysis.

Our study shows that the distribution of coronary risk factors varies across age groups. Overweight and smoking were more prevalent in the younger age groups, whereas diabetes and hypertension were more common among older patients. This may be explained by the later manifestation of diabetes and hypertension in life. The reverse association between BMI and age and the association between BMI and prevalence of coronary risk factors, supports the role of overweight and obesity in the pathogenesis of metabolic dysfunction and coronary

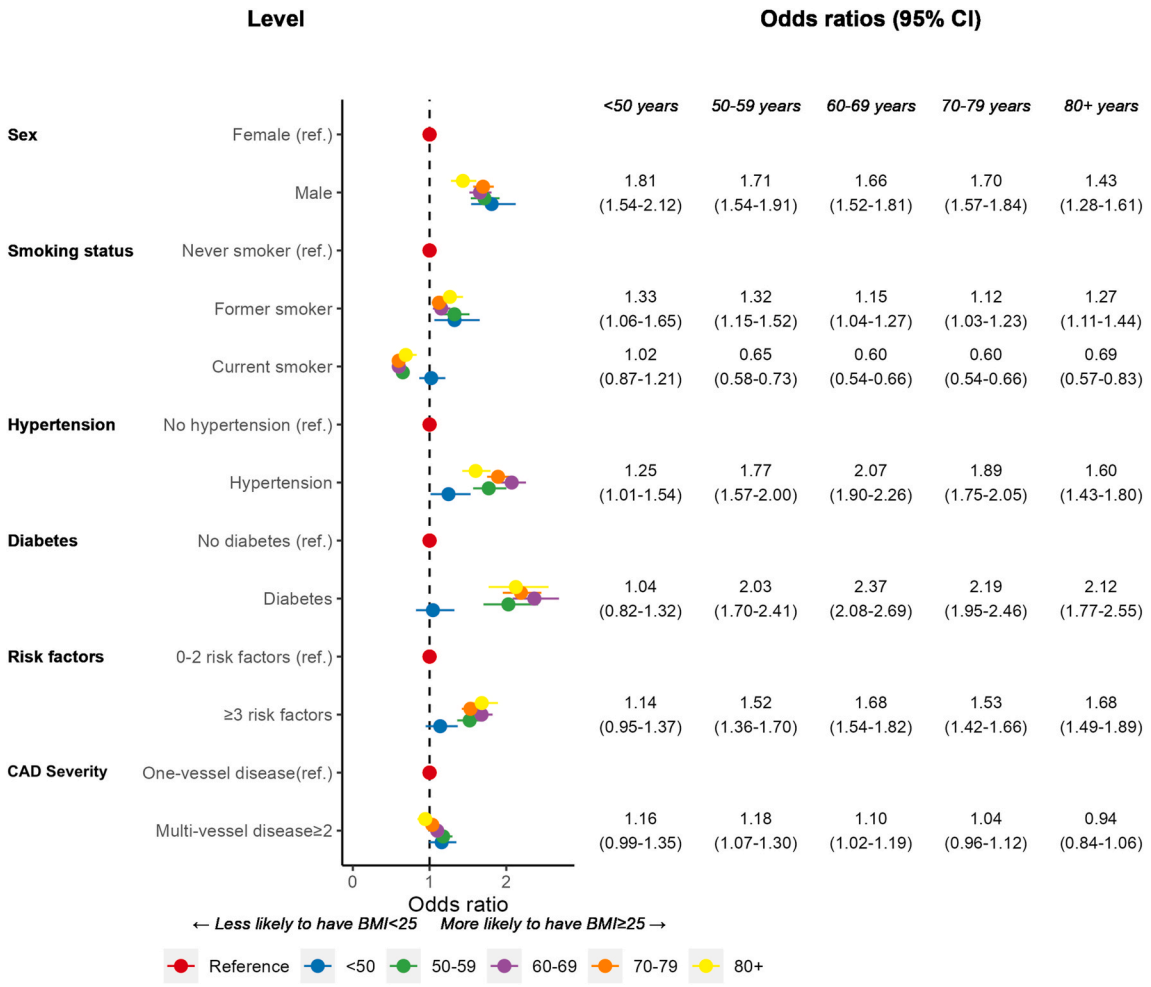

Fig. 3. OR for the association between BMI, coronary risk factors and multivessel disease stratified by age groups. OR are adjusted for sex. CAD = coronary artery disease.

Table 2
Odds ratio for the presence of multivessel disease.

Risk factor	Univariate OR [95 % CI]	*p*-value	Multivariate model[a] OR [95 % CI]	*p*-value
BMI ≥25 kg/m²	1.08 [1.03; 1.12]	<0.001	1.01 [0.97; 1.05]	0.74
<50 years	Reference	<0.001	Reference	<0.001
50–59 years	1.36 [1.26; 1.48]		1.33 [1.23; 1.44]	
60–69 years	2.05 [1.90; 2.21]		1.93 [1.79; 2.08]	
70–79 years	2.55 [2.37; 2.75]		2.43 [2.25; 2.63]	
>80 years	2.91 [2.67; 3.18]		2.96 [2.70; 3.25]	
Male sex	1.35 [1.29; 1.41]	<0.001	1.52 [1.45; 1.59.]	<0.001
Diabetes	1.70 [1.61; 1.80]	<0.001	1.53 [1.44; 1.62]	<0.001
Hypertension	1.55 [1.49; 1.61]	<0.001	1.29 [1.24; 1.35]	<0.001
Never smoker	Reference		Reference	
Current	0.91 [0.87; 0.96]	<0.001	1.14 [1.09; 1.26]	<0.001
Former	1.25 [1.20; 1.31]	<0.001	1.11 [1.05; 1.16]	<0.001

BMI: Body mass index, CI: confidence interval, OR: Odds ratio.
[a] Multivariate model adjusted for BMI, age categories, sex, diabetes, hypertension, and smoking status.

artery disease [10]. Increased BMI may affect coronary artery disease through intermediate coronary risk factors like hypertension, diabetes, and dyslipidemia. In our study, the substantial role of smoking on the increased risk of coronary artery disease is underscored. This is substantiated by the predominance of current smokers within the lower BMI categories, while former smokers are more prevalent in the higher BMI categories. Furthermore, our study shows that roughly half of the patients <50 years were current smokers, irrespective of BMI. This finding supports the role of smoking in causing early coronary artery disease even in the absence of overweight or obesity and its associated risk factors.

Others studies have shown similar results regarding BMI, age, and coronary risk factors [28–30]. These studies have found that in higher BMI-categories, a higher prevalence of diabetes, hypertension, and hyperlipidemia were found. Furthermore, overweight patients were younger compared to normal weight and underweight patients. Formentini et al. [31] reported the same association between BMI and age. They also observed that underweight patients with coronary artery disease were older compared to patients with overweight and obesity.

Previous studies have reported better clinical outcome in patients with overweight or obesity compared to patients with normal weight treated for coronary artery disease. This phenomenon is known as "the obesity paradox" [18,19]. There may be several explanations for the obesity paradox. Importantly, the obesity paradox may be a result of the collider bias introduced by only examining patients with coronary artery disease [32]. Accordingly, it has been reported that 1) patients with obesity are characterized by being younger than patients with normal

weight, and 2) current smokers are often overrepresented amongst patients with normal weight [18,33]. Both of these associations are supported by the findings in our study. Moreover, we found no correlation between multivessel disease and BMI, which can also be a contributing factor to the paradox, as pointed out by Gregory et all [34]. In the setting of the current obesity epidemic, further research is acutely needed to enhance our understanding of the relation between obesity and coronary artery disease. Long-term general population studies, and mechanistic and larger cardiovascular outcome studies of the impact of medications directed against the metabolic dysfunction seen in overweight and obesity are likely to enhance our understanding of this field.

The observed negative association between BMI and smoking in our study could possibly be attributed to a collider bias caused by our inclusions criteria, underscoring the importance of the two variables. However, it remains plausible that smoking contributes to weight loss. Previous studies have shown that current smokers is less likely to be overweight or obese compared to former smoker, due to the tendency to weight gain in patients after smoking cessation [35–37].

The missing association between BMI and multivessel disease was also observed in other studies [38–40]. Amin et al. [38] reported that BMI was not an independent predictor of the severity of coronary artery disease in multivariate analysis. However, the severity of coronary artery disease was associated with the presence of diabetes, like in our data. Supporting our findings, Khan et al. [41] observed that a high level of HbA1c was associated with an increased severity of coronary artery disease. Our study observed an association between multivessel disease and the presence of diabetes, hypertension, and smoking status. This finding underscores the impact of metabolic dysfunction and the clustering of coronary risk factors on developing coronary artery disease independent of BMI [8].

To our knowledge, our study provides the largest, nationwide, and contemporary analysis of a population of patients with invasively diagnosed obstructive coronary artery disease. Due to the large sample size in our study, our results gain increased applicability and generalizability.

4.1. Strengths and limitations

Use of The Danish Nationwide registries allowed inclusion regardless of socioeconomic status, education, geography, and health insurance. For that reason, our study has low selections bias.

Furthermore, previous validation studies have demonstrated high coverage, completeness and high positive predictive values for coronary artery disease, invasive procedures, and comorbidities, underpinning the reliability and accuracy of the data used [23,42–44]. As mentioned earlier, due to our inclusion criteria of only including patients with a first-time diagnosis of coronary obstructive disease, rather than patients from the general population, this selection complicates the study of associations between risk factors. Coronary artery disease has already manifested at baseline, and important independent risk factors may show a spurious negative correlation resulting from collider bias [45]. Our study is observational, and our findings cannot prove causation between BMI and coronary artery disease. Additional limitations are the utilization of only BMI as a measurement for overweight and obesity. Although BMI is a widely used measurement, the use of BMI as a measurement for overweight and obesity is problematic given its inability to differentiate between adipose and lean tissue and between visceral and over-all adiposity. According to several organizations and expert panels, use of thigh waist circumference ratio (WC) with BMI is recommended but this is not collected in any of the registries. WC is a measurement of abdominal obesity, which is associated with increasing risk for coronary artery disease [14].

Another limitation relates to the smoking status. The Danish heart registry does not contain information on smoking duration, pack(s) per day, or years since smoking cessation among former smokers. All these factors would contribute to a more accurate assessment of smoking status. Furthermore, we lack information regarding HbA1c, lipid levels, socioeconomic status, alcohol consumption and physical activity, all which could further contribute to assessing the patients' risk profile. Misclassification of ICD-10 codes may be site-specific and thus be prone to under- and overcoding. However, a previous study found substantial homogeneity across Danish regions regarding key sociodemographic and health related characteristics, suggesting that the risk of this may be small [46]. In our study, prescribed medication was only considered valid up to a maximum of six months prior to the patients undergoing ICA. This may have led to some patients being prescribed statins during their investigation of coronary artery disease, potentially resulting in an overestimation of statin usage for primary prevention purposes. Furthermore, the presence of diabetes and hypertension among patients was determined based on their use of antidiabetic medications and at least minimum two antihypertensives, respectively. However, this definition is not without limitations, as it may overlook patients who are prediabetic, or patients who solely rely on a single antihypertensive medication or lifestyle interventions as treatment for their hypertension. This could result in the underdiagnosis of diabetes and hypertension.

4.2. Perspectives

Our findings highlight the role of overweight-associated risk factors and smoking, as contributors to the development of coronary artery disease. In light of these findings, important approaches to prevent coronary artery disease are through the management of overweight and obesity, by advocating for a balanced diet, regular physical activity, weight management and through advocating against smoking and encouraging smoking cessation [47]. Particularly focusing preventive strategies on reducing obesity seems to the most critical area, as average BMI is rising over the study period. Prevention strategies should be implemented at both the general population level and the individual level specifically targeting patients with high risk for developing coronary artery disease [48].

5. Conclusion

Among all patients receiving a first-time invasive diagnosis of obstructive coronary disease in Denmark in the years 2012–2018, 66.3 % were overweight or obese. Young patients generally had higher BMI and were more likely to be current smokers. Overweight or obesity was strongly associated with the presence of diabetes and hypertension. Among patients with normal weight or underweight, there was a high proportion of current smokers. BMI was not independently associated with the presence of multivessel disease.

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Conflict of interest

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Data availability

The data underlying this paper were provided by Statistics Denmark. Access to data requires granted permission.

CRediT authorship contribution statement

Maria Hang Xuan Pham: Writing – Original Draft, Writing – review & editing, Conceptualization, Software, Formal analysis, Data curation, Project administstration, Visualization. **Daniel Mølager Christensen:** Writing – review & editing, Software, Formal analysis, Data curation.

Andreas Torp Kristensen: Writing – review & editing. **Charlotte Middelfart:** Writing – review & editing. **Caroline Sindet-Pedersen:** Writing – review & editing, Formal analysis, Data curation. **Gunnar Gislason:** Writing – review & editing, Conceptualization. **Niels Thue Olsen:** Writing – review & editing, Supervision, Data curation, Conceptualization, Validation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200299.

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