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Original Article

The Importance of Nontraditional and Sex-Specific Risk Factors in Young Women With Vasomotor Nonobstructive vs Obstructive Coronary Syndromes

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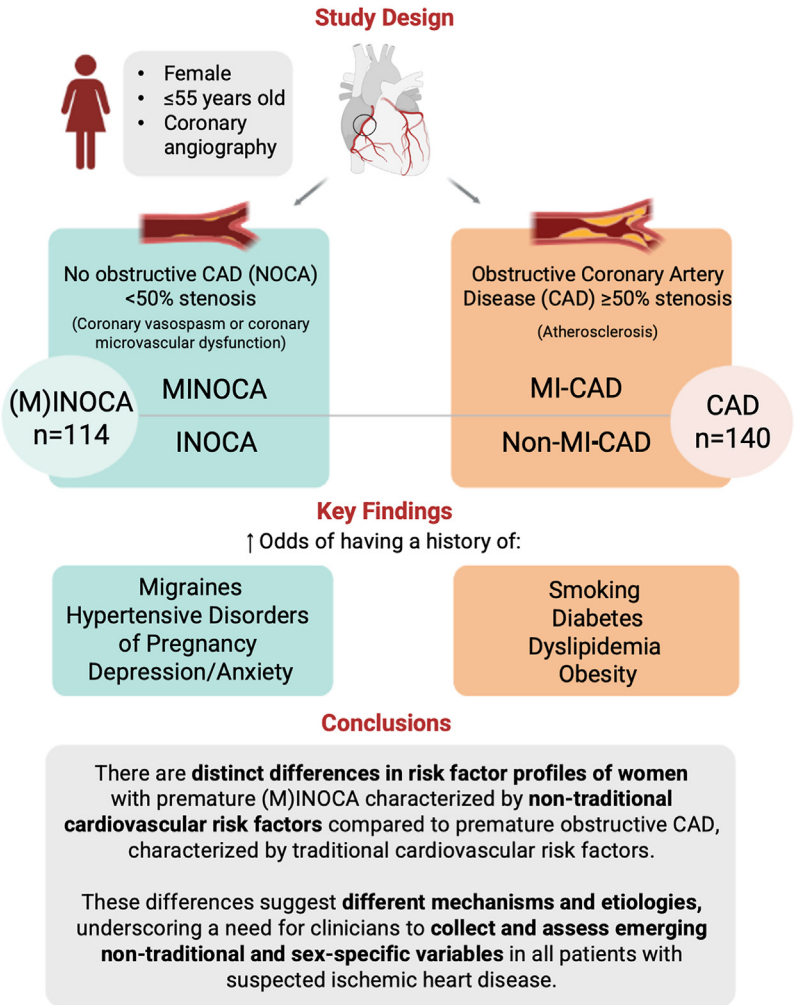

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ABSTRACT

Background: Heart disease is the leading cause of premature death for women in Canada. Ischemic heart disease is categorized as myocardial infarction (MI) with no obstructive coronary artery disease (MINOCA), ischemia with no obstructive coronary arteries (INOCA), and atherosclerotic obstructive coronary artery disease (CAD) with MI (MI-CAD) or without MI (non-MI-CAD). This study aims to study the prevalence of traditional and nontraditional ischemic heart disease risk factors and their relationships with (M)INOCA, compared to MI-CAD and non-MI-CAD in young women.

Methods: This study investigated women who presented with premature (at age $\leq$ 55 years) vasomotor entities of (M)INOCA or obstructive CAD confirmed by coronary angiography, who are currently enrolled in either the Leslie Diamond Women's Heart Health Clinic Registry (WHC) or the **S**tudy to **A**void Cardiovascular **E**vents in **B**ritish **C**olumbia (SAVEBC). Univariable and multivariable regression models were applied to investigate associations of risk factors with odds of (M)INOCA, MI-CAD, and non-MI-CAD.

Results: A total of 254 women enrolled between 2015 and 2022 were analyzed, as follows: 77 with INOCA and 37 with MINOCA from the registry, and 66 with non-MI-CAD and 74 with MI-CAD from the study. Regression analyses demonstrated that migraines and preeclampsia or gestational hypertension were the most significant risk factors, with a higher likelihood of being associated with premature (M)INOCA, relative to obstructive CAD. Conversely, the presence of diabetes and a current or previous smoking history had the highest likelihood of being associated with premature CAD.

Conclusions: The risk factor profiles of patients with premature (M)INOCA, compared to obstructive CAD, have significant differences.

RÉSUMÉ

Contexte : Au Canada, la cardiopathie est la principale cause de décès prématuré chez les femmes. La cardiopathie ischémique est catégorisée comme suit : infarctus du myocarde (IM) en l'absence de coronaropathie obstructive (MINOCA), ischémie sans obstruction des artères coronaires (INOCA) et athérosclérose coronaire obstructive accompagnée d'un IM ou sans IM. La présente étude vise à examiner la prévalence des facteurs de risque classiques et non classiques de cardiopathie ischémique et leurs liens avec le (M)INOCA, comparativement à l'athérosclérose coronaire obstructive accompagnée d'un IM ou sans IM chez les femmes jeunes.

Méthodologie : Cette étude portait sur des femmes qui avaient prématurément (55 ans ou moins) souffert d'un (M)INOCA ou d'une coronaropathie obstructive confirmés par coronarographie et qui étaient inscrites au registre de la Leslie Diamond Women's Heart Health Clinic (WHC) ou qui participaient à l'étude visant à éviter les événements cardiovasculaires en Colombie-Britannique (***S**tudy to **A**void Cardiovascular **E**vents in **BC***; SAVEBC). Des modèles de régression univariés et multivariés ont été utilisés pour explorer les associations entre les facteurs de risque et les probabilités de (M)INOCA, ainsi que d'athérosclérose coronaire obstructive accompagnée ou non d'un IM.

Résultats : Au total, 254 femmes inscrites de 2015 à 2022 ont été recensées, soit 77 présentant une INOCA et 37, un MINOCA selon le registre WHC, et 66 présentant une athérosclérose coronaire obstructive sans IM et 74, une athérosclérose coronaire obstructive accompagnée d'un IM selon l'étude SAVEBC. Les analyses de régression ont démontré que les migraines et la prééclampsie ou l'hypertension gestationnelle étaient les facteurs de risque les plus importants associés à une probabilité la plus élevée de (M)INOCA comparativement à une coronaropathie obstructive. En revanche, la présence d'un diabète et d'un tabagisme actuel ou passé était associée à la probabilité la plus élevée de coronaropathie prématurée.

Conclusions : Il existe d'importantes différences pour ce qui est des profils de facteurs de risque des patientes ayant prématurément souffert d'un (M)INOCA en comparaison d'une coronaropathie obstructive.

Lay Summary

Risk factors were compared in 2 groups of young women with heart disease—those with plaque obstructing blood flow in the heart's blood vessels (obstructive 'coronary artery disease' [CAD]), and those with abnormal expansion or contraction of the blood vessels, but no obstruction of blood flow (no obstructive CAD). The risk factors—history of migraines, elevated blood pressure during pregnancy, and depression and/or anxiety—were significantly more common in the group with no obstructive CAD.

Ischemic heart disease (IHD) is a leading cause of preventable death of women in Canada.[1] Concerning data show that, over the past 2 decades, incidence rates have not been declining in younger women.[2] The prevalence of several traditional modifiable cardiovascular (CV) risk factors (diabetes, hypertension, and obesity) has been rising steadily in young women in British Columbia (BC) over the past 2 decades,[3] but the degree to which these risk factors explain the lack of decline of IHD rates in young women is unclear. Momentum has been growing toward studying the relative contributions of "nontraditional" CV risk factors and female-specific risk factors to IHD etiologies. A recent review by the Canadian Women's Heart Health Alliance describes the higher relative risk of IHD in women, compared to men, who have diagnoses of risk factors such as depression, autoimmune disorders, and female-specific pathologies such as preeclampsia.[4]

Nonobstructive IHD entities, including myocardial infarction (MI) with no obstructive coronary arteries (MINOCA) and ischemia with no obstructive coronary arteries (INOCA), are heterogenous syndromes of IHD characterized by normal or unobstructed epicardial vessels (< 50% stenosis in any epicardial artery). MINOCA accounts for approximately 6% of patients presenting with acute coronary syndrome and is 3 times more prevalent in women presenting with MI (10.5%) than in men (3.5%).[5] Up to two thirds of angiograms performed for women with suspected cardiac ischemia reveal

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See page 289 for disclosure information.

INOCA, a prevalence that is twice as high as that observed in men.[6] Women who suffer a MINOCA or INOCA [(M)INOCA] event do not follow a benign clinical course: a study of patients in BC undergoing coronary angiography between 1999 and 2002 showed that the risk of major adverse cardiovascular events (MACE) in women with stable angina and nonobstructive coronary artery disease (CAD) was almost 3 times higher than that in men with nonobstructive CAD in the first year following coronary angiography.[7]

Underlying vasomotor etiologies of (M)INOCA consist predominantly of coronary vasospasm and coronary microvascular dysfunction (CMD),[8] entities that affect the epicardial arteries (> 400 μm) and microvasculature (100-400-μM pre-arterioles, < 100-μM arterioles, and < 10-μm capillaries), respectively. Prevalence estimates of vasospasm and CMD are lacking in a population of women with premature IHD: CMD was identified through invasive coronary reactivity testing in approximately 50% of women with INOCA in the **W**omen's **I**schemia **S**yndrome **E**valuation (WISE) multicentre prospective study, which followed over 900 clinically stable women (all ages) referred for coronary angiography between 1996 and 2006.[9] A study by Sara et al.[10] identified vasospasm as the responsible etiology for approximately 30% of patients who had nonobstructive CAD undergoing coronary functional testing at the Mayo Clinic catheterization lab between 1993 and 2012. These entities remain vastly understudied, underrecognized, and undertreated, compared to obstructive CAD. This paucity in recognition may be attributed to the heterogeneity of the entities, the lack of robust clinical trials,[11] the lower level of knowledge about these conditions by practitioners, and the difficulty in obtaining specialized testing to make these diagnoses.[12]

Studies have shown that women presenting with premature acute MI (< 55 years old) have differences in risk factor profiles, treatment patterns, and excess mortality rates, compared with those for similarly aged men[3] and older women.[13] This difference may be due in part to a higher prevalence and/or differing effect sizes of traditional and nontraditional CV risk factors in this group, such as higher prevalence and associated risk of MI in younger women with diabetes, compared to men or their older counterparts.[14] For example, sex differences have been observed in the prevalence of major CV risk factors, such as hypertension, dyslipidemia, diabetes, and smoking, and other risk enhancers.[15-17] Furthermore, Safdar et al.[18] (2018) found fewer traditional risk factors in women with premature MINOCA, compared to women with MI and obstructive CAD (MI-CAD) in the **V**ariation **i**n **R**ecovery: Role of **G**ender on **O**utcomes of Young acute MI Patients (VIRGO) study. These studies do not clarify the extent to which similar conclusions may also extend to women with INOCA and CAD with no MI (non-MI-CAD).

Given the paucity of data on (M)INOCA in young women, and the respective contributing risk factors, we sought to compare the prevalence of traditional and nontraditional risk factors in women with premature presentations of (M)INOCA and obstructive CAD, with or without MI. We specifically chose to focus on vasomotor etiologies of (M)INOCA given the heterogeneity of these entities and the extensive prior work done on other etiologies of (M)INOCA, such as spontaneous coronary artery dissection (SCAD).[19,20]

Materials and Methods

Study population

This study included women with (M)INOCA enrolled in the Leslie Diamond Women's Heart Health Clinic Registry (WHC) and women with obstructive CAD in the **S**tudy to **A**void Cardio**v**ascular **E**vents in BC (SAVEBC) biobank.

Eligibility criteria for this study were met if women from either study had signs and symptoms of ischemia and/or an acute coronary syndrome and had undergone coronary angiography (CA) and/or cardiac CT angiography (CTA) before or at age 55 years to delineate their coronary anatomy. The earliest date of CA/CTA was February 1995 for the WHC and September 2015 for SAVEBC; the last date for both cohorts was July 10, 2022.

For the WHC, women with MINOCA or INOCA and final diagnoses of definite or probable coronary vasospasm or CMD were included. MINOCA was defined per the 2019 scientific statement from the American Heart Association,[21] and INOCA was defined per the 2020 European Society of Percutaneous Cardiovascular Interventions (EAPCI) expert consensus document on ischemia with nonobstructive coronary arteries.[22] Probable and confirmed CMD and coronary vasospasm were defined using the **Co**ronary **Va**somotion **D**isorder **I**nternational **S**tudy (COVADIS) group definition.[23] WHC patients were excluded if their diagnosis after the first CA/CTA was obstructive CAD, non-(M)INOCA cardiac (or noncardiac) entities (ie, arrythmia, esophageal spasm), or if the final diagnoses were those other than vasomotor etiologies (ie, SCAD). For the SAVEBC study, female patients with obstructive CAD (defined as any epicardial vessel with ≥ 50% stenosis) were included in this study. SAVEBC patients were excluded if their presentation had any nonatherosclerotic component (ie, SCAD, vasospasm).

The WHC is a quaternary outpatient cardiology clinic located at Vancouver General Hospital in BC, Canada, comprising a multidisciplinary team of cardiologists, nurse practitioners, and a psychiatrist specializing in women's heart health. The clinic has access to specialized testing for (M)INOCA, including coronary reactivity testing, optical coherence tomography (OCT), and adenosine cardiac magnetic resonance imaging (MRI). The WHC registry began recruitment of patients referred to the clinic in 2016 and has 322 patients enrolled, of which 259 patients (80%) have (M)INOCA. Data are collected from physician consult notes and diagnostic test reports uploaded to electronic medical records, including information about comorbidities (including CV risk factors) and cardiac presentation characteristics.

The SAVEBC biobank began recruitment in 2015 and is a prospective study of patients who present with premature CAD with stenosis of at least 50% in at least one epicardial artery at age ≤ 50 years for male patients and age ≤ 55 years for female patients. A detailed description of the study design and rationale is provided elsewhere.[24] Briefly, and in contrast to those in the WHC, patients in the SAVEBC study were recruited from cardiac catheterization laboratories and cardiology wards at Vancouver General Hospital, St. Paul's

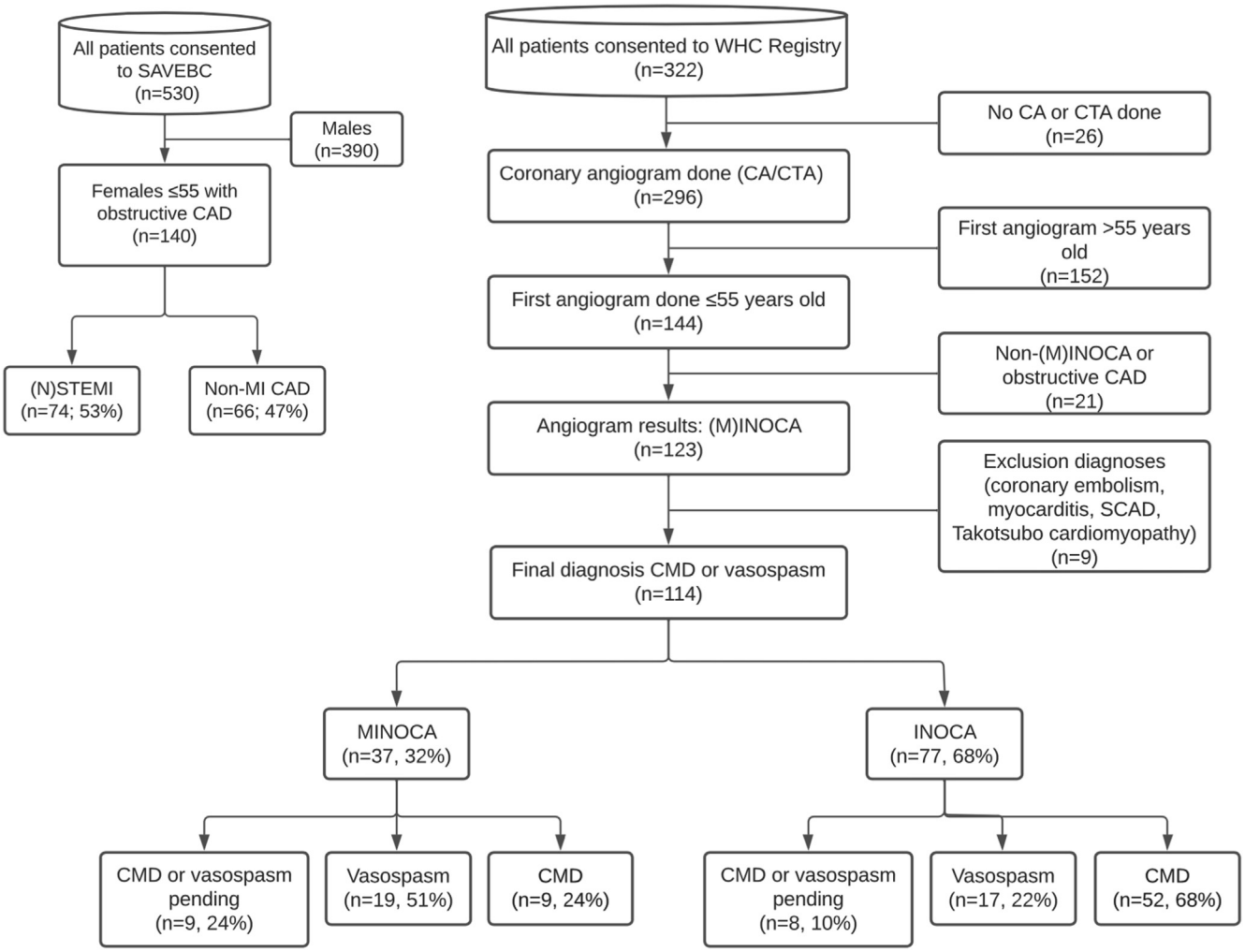

Figure 1. Flow diagram of exclusion steps by which eligible **S**tudy to **A**void Cardio**v**ascular **E**vents in **B**ritish **C**olumbia (SAVEBC) and Leslie Diamond Women's Heart Health Clinic Registry (WHC) patients were filtered. CA, coronary angiogram; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CTA, computed tomography coronary angiogram; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries; (M)INOCA, MINOCA or INOCA; (N)STEMI, (non-)ST-elevation myocardial infarction; SCAD, spontaneous coronary artery dissection; WHC, Leslie Diamond Women's Heart Health Clinic Registry.

Hospital (Vancouver, BC) and Kelowna General Hospital (Kelowna, BC). The SAVEBC study also collects information on CV risk factors, comorbidities, presentation characteristics, physical examination, and laboratory test results. This information is collected directly from patients during the study visits and from paper-based and electronic medical records, including medical charts, and pharmacy dispensing records. In addition, reports are collected from the Cardiac Services BC Registry, a province-wide electronic information system collecting information on all patients who have received cardiac procedures (coronary angiography, percutaneous coronary interventions, coronary artery bypass surgery, valve procedures, and implantable devices) in the province.

Patient data

Shared demographic and clinical covariates that are collected in both cohorts were identified and then extracted. Variable names and definitions were standardized prior to merging the 2 datasets.

Sociodemographic variables were consolidated between patient self-report on study questionnaires and any mention in physician consult notes. Self-reported race (Caucasian, South Asian, East Asian, First Nations, African-Canadian, and Other) was summarized as Caucasian or non-Caucasian due to the high proportions of Caucasians in both cohorts. Partnered status was recorded as partnered (married or common law) or not partnered (single, divorced, or widowed).

Traditional CV risk factors included the following: dyslipidemia (total cholesterol $\geq$ 240 mg/dL [6.2 mmol/L], low-density lipoprotein cholesterol $\geq$ 160 mg/dL [4.1 mmol/L], high-density lipoprotein cholesterol $\leq$ 40 mg/dL [1.0 mmol/L]; triglycerides $\geq$ 200 mg/dL [2.3 mmol/L], or treatment of dyslipidemia[25]); hypertension (systolic/diastolic blood pressure $\geq$ 140/90 mm Hg per the Canadian hypertension guidelines[26]); diabetes (type 1 or 2: fasting plasma glucose $\geq$ 126 mg/dL (7 mmol/L) in at least 2 baseline measurements, hemoglobin A1c $\geq$ 6.5%, physician diagnosis, or treatment of diabetes[27]);

Table 1. Frequencies of risk factors in the Leslie Diamond Women's Heart Health Clinic Registry (WHC) and Study to Avoid Cardiovascular Events in British Columbia (SAVEBC) cohorts further stratified by diagnostic subgroups (MINOCA, INOCA, MI-CAD, non-MI-CAD)

	WHC		SAVEBC				
Variable	MINOCA at age ≤ 55 y (n = 37)	INOCA at age ≤ 55 y (n = 77)	MI-CAD at age ≤ 55 y (n = 74)	Non-MI CAD at age ≤ 55 y (n = 66)	WHC (n = 114)	SAVEBC (n = 140)	*P* (WHC vs SAVEBC)
Age at first CA/CTA, y (IQR)	49 (42, 55)	50 (41, 55)	50 (44, 55)	50.5 (44.5, 55)	49 (41, 55)	50 (44, 55)	0.08
Race							
Caucasian ("White")	24 (65)	56 (73)	30 (41)	27 (41)	80 (70)	57 (41)	< 0.01
Non-Caucasian	11 (30)	20 (26)	29 (39)	25 (38)	31 (27)	54 (39)	
South Asian	2 (5)	7 (9)	7 (9)	5 (8)	9 (8)	12 (9)	
East Asian ("Chinese, Japanese, Korean")	5 (14)	2 (3)	5 (7)	4 (6)	7 (6)	9 (6)	
First Nations ("Aboriginal")	0	2 (3)	6 (8)	2 (3)	2 (2)	8 (6)	
African-Canadian ("Black")	0	1 (1)	0	0	1 (1)	0	
Other (including mixed race)	4 (11)	8 (10)	11 (15)	14 (21)	12 (11)	25 (18)	
Missing*	2 (5)	1 (1)	15 (20)	14 (21)	3 (3)	29 (21)	
Partnered (married, common law)	36 (97)	61 (79)	36 (49)	32 (48)	97 (85)	68 (49)	< 0.01
Missing	0	0	18 (24)	20 (30)	0	38 (27)	
Dyslipidemia	14 (38)	39 (51)	46 (62)	48 (73)	53 (46)	94 (67)	< 0.001
Diabetes	3 (8)	10 (13)	24 (32)	22 (33)	13 (11)	46 (33)	< 0.001
Type 1	0	2 (3)	0	2 (3)	2 (2)	2 (1)	
Type 2	3 (8)	8 (10)	24 (32)	20 (30)	11 (10)	44 (31)	
Gestational diabetes	3 (8)	8 (10)	9 (12)	16 (24)	11 (10)	25 (18)	
Hypertension	13 (35)	30 (39)	42 (57)	34 (52)	43 (38)	76 (54)	< 0.01
Obesity (BMI ≥ 30)	8 (22)	17 (22)	35 (47)	26 (39)	25 (22)	61 (44)	< 0.001
Missing	0	0	5 (7)	1 (2)	0	6 (4)	
Smoking history							
Never	33 (89)	66 (86)	34 (46)	38 (58)	99 (87)	72 (51)	< 0.001
Current	1 (3)	2 (3)	17 (23)	9 (14)	3 (3)	26 (19)	
Previous	3 (8)	9 (12)	23 (31)	19 (29)	12 (11)	42 (30)	
Family history of premature CVD	16 (43)	31 (40)	31 (42)	32 (48)	47 (41)	63 (45)	0.1
Missing	0	0	15 (20)	5 (8)	0	20 (14)	
Depression and/or anxiety	13 (35)	26 (34)	22 (30)	19 (29)	39 (34)	41 (29)	0.54
Hypothyroidism	2 (5)	14 (18)	12 (16)	10 (15)	16 (14)	22 (16)	0.6
Migraines	19 (51)	23 (30)	2 (3)	5 (8)	42 (37)	7 (5)	< 0.001
Autoimmune disorder(s) (any)	3 (8)	14 (18)	18 (24)	12 (18)	17 (15)	30 (21)	0.21
Preeclampsia or gestational hypertension	7 (19)	6 (8)	3 (4)	2 (3)	13 (11)	5 (4)	0.04
Missing	4 (11)	10 (13)	19 (26)	15 (23)	14 (12)	34 (24)	
Number of children							
0 or 1	8 (22)	12 (16)	21 (28)	21 (32)	20 (18)	42 (30)	0.04
2 or 3	22 (59)	50 (65)	36 (49)	31 (47)	72 (63)	67 (48)	
4+	3 (8)	5 (6)	6 (8)	3 (5)	8 (7)	9 (6)	
Missing	4 (11)	10 (13)	11 (15)	11 (17)	14 (12)	22 (16)	
Number of nonterm pregnancies							0.68
0	18 (49)	25 (32)	32 (43)	33 (50)	43 (38)	65 (46)	
1	7 (19)	16 (21)	16 (22)	14 (21)	23 (20)	30 (21)	
2+	2 (5)	18 (23)	14 (19)	8 (12)	20 (18)	22 (16)	
Missing	10 (27)	18 (23)	12 (16)	11 (17)	28 (25)	23 (16)	

Values are n (%), unless otherwise indicated.

BMI, body mass index; CA, coronary angiogram; CAD, coronary artery disease; CTA, computed tomography coronary angiogram; CVD, cardiovascular disease; INOCA, ischemia with no obstructive coronary arteries; IQR, interquartile range; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries.

*Missing proportions provided when > 5%.

family history of premature CV disease (CVD; age < 55 years for men, < 65 years for women); obesity (body mass index ≥ 30 kg/m^2); and smoking (former, current, or never).

Nontraditional clinical risk factors and female-specific risk modifiers included the following: history of a clinical diagnosis of depression and/or anxiety, hypothyroidism, diagnosis of migraines (with or without aura), diagnosis of an autoimmune disease, preeclampsia (gestational systolic/diastolic blood pressure ≥ 140/90 mm Hg and proteinuria per the American College of Obstetricians and Gynecologists guidelines[28]) or gestational hypertension, gestational diabetes, number of children (0-1, 2-3, 4+), and number of nonterm pregnancies, such as miscarriage, abortion, and/or stillbirth (0, 1, or 2+).

Table 2. Traditional cardiovascular risk factors stratified by cohort (Study to Avoid Cardiovascular Events in British Columbia [SAVEBC] vs Leslie Diamond Women's Heart Health Clinic Registry [WHC]) and by diagnostic subgroup (MI-CAD, non-MI-CAD, MINOCA, INOCA)

		Traditional cardiovascular risk factors*, n (%)						
Cohort	Diagnosis	0	1	2	3	4	5	6
WHC	MINOCA	5 (13.5)	15 (40.5)	10 (27.0)	6 (16.2)	0	1 (2.7)	0
	INOCA	17 (22.1)	19 (24.7)	15 (19.5)	16 (20.8)	9 (11.7)	1 (1.3)	0
	Total	22 (19.3)	34 (29.8)	25 (21.9)	22 (19.3)	9 (7.9)	2 (1.8)	0
SAVEBC	MI-CAD	3 (4.1)	8 (10.8)	16 (21.6)	23 (31.1)	13 (17.6)	9 (12.2)	2 (2.7)
	Non-MI-CAD	2 (3.0)	9 (13.6)	14 (21.2)	20 (30.3)	14 (21.2)	5 (7.6)	2 (3.0)
	Total	5 (3.6)	17 (12.1)	30 (21.4)	43 (30.7)	27 (19.3)	14 (10.0)	4 (2.9)

CAD, coronary artery disease; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries.

*Traditional risk factors quantified were dyslipidemia, diabetes (type 1 or 2), hypertension, obesity, past or current smoker, and family history of premature cardiovascular disease.

Data analyses

Baseline characteristics were reported as medians for continuous variables, and counts with proportions for categorical variables. Cumulative burden was calculated by summing the number of traditional CV risk factors (range 0-6) and nontraditional CV risk factors (range 0-5). The main comparison was between the 2 cohorts; both cohorts were further stratified by the presence vs absence of MI. Categorical variables were compared using χ^2 tests; continuous variables were compared using the Kruskal-Wallis test.

To assess the strength of the association between each risk factor and the relevant diagnoses, several univariable logistic regression tests were conducted. The primary comparisons of interest were associations with (M)INOCA relative to any obstructive CAD. The associations between each risk factor and diagnoses were then assessed for INOCA relative to non-MI-CAD, and MINOCA relative to MI-CAD, with the associations expressed as odds.

Iterative, multivariable logistic regression models were constructed to identify factors independently associated with (M)INOCA compared to any obstructive CAD. In the first model, covariates were selected based on clinical importance, as follows: age at earliest angiography; diabetes (type 1 or type 2); hypertension; depression and/or anxiety; and family history of premature CVD. In the second model, the 3 variables with the strongest effect sizes in the univariable analysis were added to the model—preeclampsia and/or gestational hypertension, smoking status, and migraines. Log likelihood changes, Akaike's criterion, and the number of degrees of freedom were assessed to optimize the model fit.

Results

Baseline characteristics

A total of 114 women from the WHC cohort had premature (M)INOCA from a vasomotor entity (n = 37 MINOCA; n = 77 INOCA), and 140 women from the SAVEBC cohort had premature obstructive CAD (n = 74 MI-CAD; n = 66 non-MI-CAD) and met the inclusion criteria, as shown in Figure 1.

In the WHC cohort, most women with MINOCA had probable or definite vasospasm (19; 51%); the rest had probable or definitive CMD (9; 24%) or an undetermined diagnosis of probable CMD or vasospasm still awaiting final testing, but with non-vasomotor entities ruled out (9; 24%). Most women with INOCA had CMD (52; 68%), and the rest had vasospasm (17; 22%) and an undetermined diagnosis of CMD or vasospasm (8; 10%). In the SAVEBC cohort, 50 women with MI-CAD presented with non-ST elevation MI (68%) and the other 24 with ST-elevation MI (32%). Among the non-MI-CAD patients, 35 presented with stable angina (53%), 22 with unstable angina (33%), and 9 with other indications for undergoing coronary angiography (14%).

Table 3. Nontraditional cardiovascular risk factors stratified by cohort (Study to Avoid Cardiovascular Events in British Columbia [SAVEBC] vs Leslie Diamond Women's Heart Health Clinic Registry [WHC]) and by diagnostic subgroup (MI-CAD, non-MI-CAD, MINOCA, INOCA)

		Nontraditional cardiovascular risk factors,* n (%)					
Cohort	Diagnosis	0	1	2	3	4	5
WHC	MINOCA	11 (29.7)	12 (32.4)	11 (29.7)	2 (5.4)	1 (2.7)	0
	INOCA	24 (31.2)	29 (37.7)	18 (25.4)	6 (7.8)	0	0
	Total	35 (30.7)	41 (36.0)	29 (25.4)	8 (7.0)	1 (0.9)	0
SAVEBC	MI-CAD	35 (47.3)	23 (31.1)	14 (18.9)	2 (2.7)	0	0
	Non-MI CAD	30 (45.5)	26 (39.4)	8 (12.1)	2 (3.0)	0	0
	Total	65 (46.4)	49 (35.0)	22 (15.7)	4 (2.9)	0	0

CAD, coronary artery disease; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries.

*Nontraditional cardiovascular risk factors quantified were depression and/or anxiety, any autoimmune disease, hypothyroidism, migraines, and preeclampsia and/or gestational hypertension.

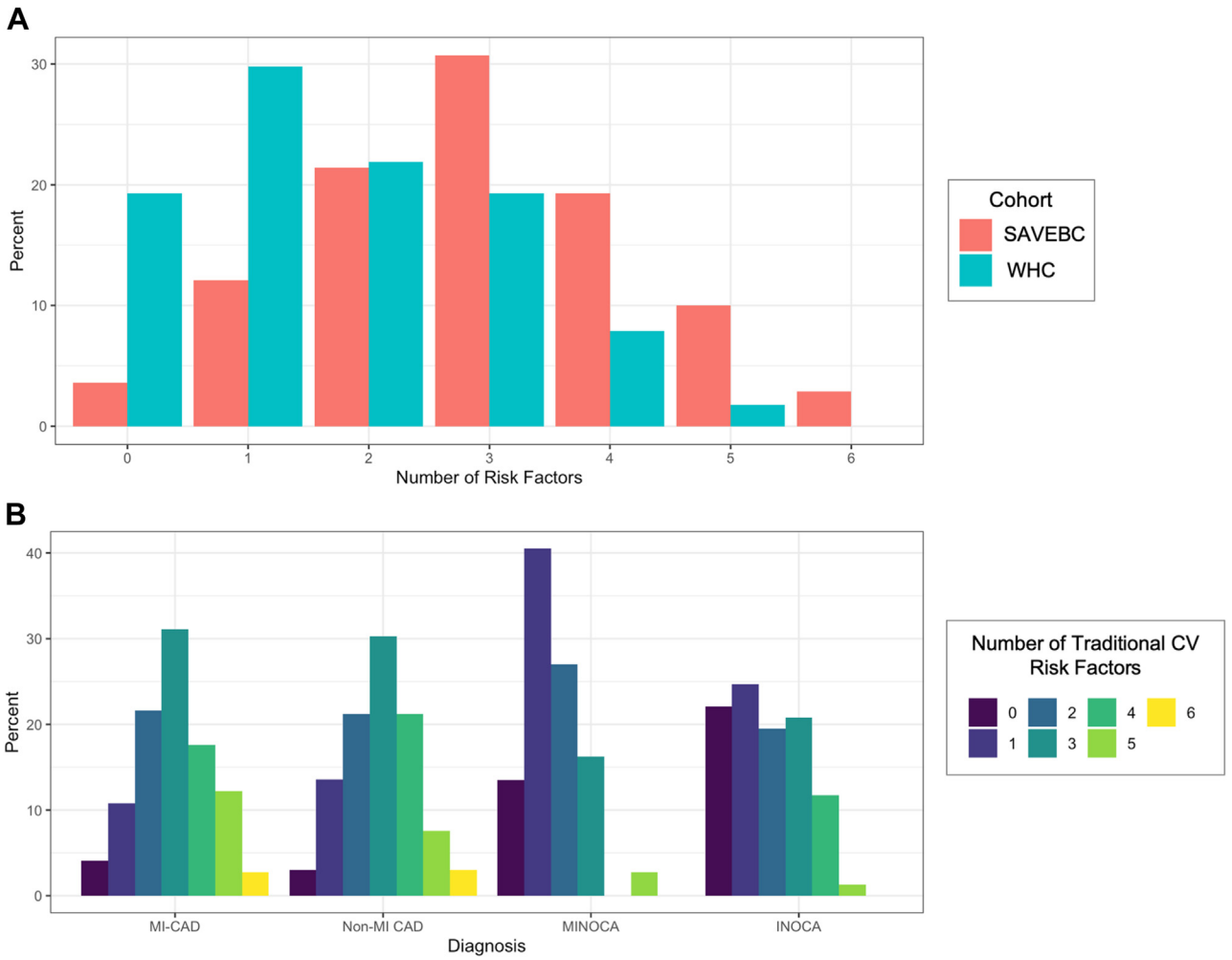

Figure 2. Histograms of total traditional cardiovascular (CV) risk factors by (**A**) cohort and (**B**) diagnostic subgroup (MI-CAD vs non-MI-CAD vs MINOCA vs INOCA). The traditional CV risk factors quantified were as follows: dyslipidemia, diabetes (type 1 or 2), hypertension, obesity, past or current smoker, and family history of premature CV disease. CAD, coronary artery disease; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries; SAVEBC, **S**tudy to **A**void Cardio**v**ascular **E**vents in **B**ritish **C**olumbia; WHC, Leslie Diamond Women's Heart Health Clinic Registry.

Risk factors

Table 1 summarizes the frequency of demographic and clinical variables across diagnostic subgroups. The median ages (interquartile range) at the first coronary angiography in each subgroup of women were 49 years (42-55 years) for those with MINOCA, 50 years (41-55 years) for those with INOCA, 50 years (44-55 years) for those with MI-CAD, and 50.5 years (44.5-55 years) for those with non-MI-CAD. Significant differences were found between women with (M)INOCA (from the WHC), compared to those with obstructive CAD (from SAVEBC) as follows: women with (M)INOCA had higher proportions of self-reported Caucasian race ($P < 0.01$); being partnered ($P < 0.01$); history of migraines ($P < 0.001$); preeclampsia or gestational hypertension ($P = 0.04$); and more children. In contrast, women with obstructive CAD had significantly higher proportions of dyslipidemia ($P < 0.001$), diabetes ($P < 0.001$), hypertension ($P < 0.01$), obesity ($P < 0.001$), and smoking history ($P < 0.001$).

The cumulative burden of traditional and nontraditional risk factors is summarized in Tables 2 and 3, respectively, with relative proportions shown in Figure 2 (traditional risk factors) and Figure 3 (nontraditional risk factors). X^2 tests comparing the cumulative burden of risk factors demonstrate significant differences between cohorts in the number of traditional risk factors (Fig. 2A; $P < 0.001$) and nontraditional risk factors (Fig. 3A; $P = 0.03$). The most frequent number of traditional risk factors seen per patient was higher for the patients with obstructive CAD (mode = 3), compared to that for women with nonobstructive CAD (mode = 1). Most strikingly, over 40% of the MINOCA group had just one traditional risk factor. The opposite trend was seen with nontraditional risk factors: in women with nonobstructive CAD, the most common number of risk factors was one; in women with obstructive CAD, the most common number was zero.

Among the 30% of women from the WHC study with only one traditional risk factor, family history of premature CVD was the most common (38%), followed by

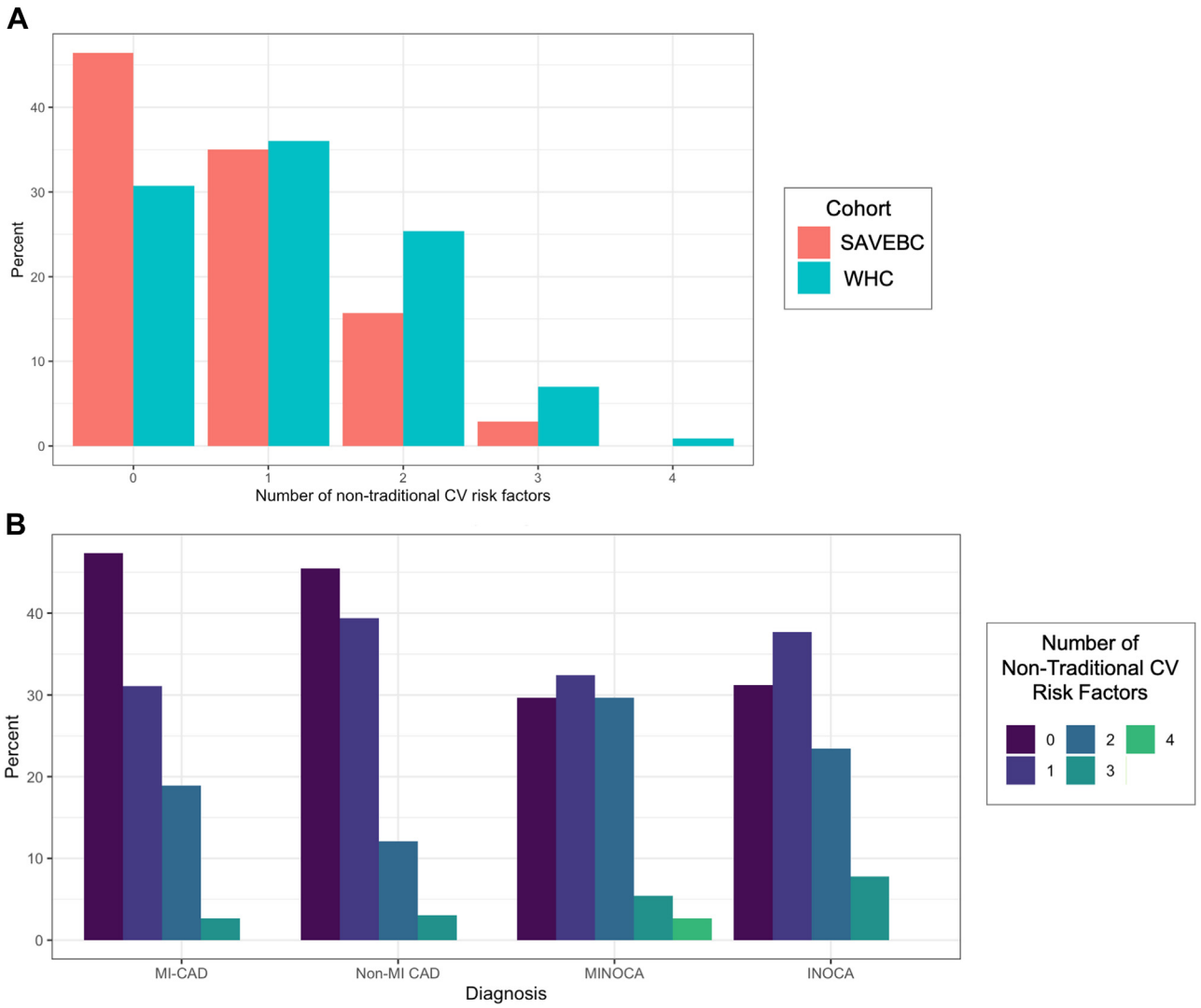

Figure 3. Histograms of total nontraditional cardiovascular (CV) risk factors by (**A**) cohort and (**B**) diagnostic subgroup (MI-CAD vs non-MI-CAD vs MINOCA vs INOCA). The nontraditional CV risk factors quantified were as follows: depression and/or anxiety, any autoimmune disease, hypothyroidism, migraines, and preeclampsia/gestational hypertension. CAD, coronary artery disease; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries; SAVEBC, **S**tudy to **A**void Cardio**v**ascular **E**vents in **B**ritish **C**olumbia; WHC, Leslie Diamond Women's Heart Health Clinic Registry.

dyslipidemia (24%), and then hypertension and obesity (15% each). Among the 12% of patients in SAVEBC with only one traditional risk factor, the most common were dyslipidemia (29%) and smoking history (29%), followed by family history of premature CVD (18%). Having 5 or 6 traditional CV risk factors was observed in over 6 times more patients in the SAVEBC cohort (12.9%) than in the WHC cohort (1.8%).

For nontraditional CV risk factors, the most frequently reported number of risk factors among WHC patients was one (36%). The most common was a history of migraines (37%), followed by depression and/or anxiety (34%) and hypothyroidism (12%). Among the SAVEBC patients, 46.5% had zero nontraditional risk factors, but among the 35% with only one nontraditional risk factor, the most common was depression and/or anxiety (45%), followed by any autoimmune disease (31%) and hypothyroidism (18%). Having 3 or 4 nontraditional CV risk factors was observed over twice as often in the WHC patients (7.9%) compared to the SAVEBC patients (2.9%)

Univariable logistic regression models

Odds ratios (ORs) and 95% confidence intervals (CIs) from the univariable regression models are summarized in Table 4. Most traditional risk factors, except for family history of CVD, were significantly associated with a reduced odds of (M)INOCA compared to any obstructive CAD, as shown in Figure 4A. The risk factors most strongly associated with an increased odds of (M)INOCA (OR $>$ 2) were history of migraines (OR 10.50 [95% CI 4.75, 26.66], $P < 0.001$); preeclampsia or gestational hypertension (OR 3.02 [95% CI

Table 4. Association between risk factors and selected diagnoses

Outcome	(M)INOCA (ref: any obstructive CAD*) OR (95% CI)	INOCA (ref: non-MI CAD) OR (95% CI)	MINOCA (ref: MI-CAD) OR (95% CI)
Sociodemographic variables			
Age at earliest CA/CTA (per y)	**0.94 (0.90, 0.99)**	0.95 (0.89, 1.00)	0.94 (0.87, 1.00)
Race: non-Caucasian	**0.41 (0.23, 0.71)**	**0.39 (0.18, 0.81)**	0.47 (0.19, 1.12)
Not partnered	**0.35 (0.18, 0.67)**	0.60 (0.26, 1.38)	**0.05 (0.00, 0.26)**
Traditional cardiovascular risk factors			
Dyslipidemia	**0.43 (0.25, 0.71)**	**0.38 (0.19, 0.78)**	**0.37 (0.16, 0.83)**
Diabetes	**0.26 (0.13, 0.50)**	**0.30 (0.13, 0.69)**	**0.18 (0.04, 0.58)**
Hypertension	**0.51 (0.31, 0.84)**	0.60 (0.31, 1.17)	**0.41 (0.18, 0.92)**
Obese (BMI $\geq$ 30)	**0.34 (0.19, 0.58)**	**0.43 (0.20, 0.88)**	**0.27 (0.10, 0.65)**
Family history of premature CVD	0.64 (0.38, 1.08)	0.62 (0.32, 1.23)	0.69 (0.30, 1.57)
Smoking history: current	**0.08 (0.02, 0.25)**	**0.13 (0.03, 0.62)**	**0.06 (0.00, 0.32)**
Smoking history: former	**0.21 (0.10, 0.41)**	**0.27 (0.11, 0.66)**	**0.13 (0.03, 0.43)**
Nontraditional risk factors and female-specific variables			
Depression and/or anxiety	1.18 (0.69, 2.01)	1.21 (0.59, 2.47)	1.18 (0.50, 2.73)
Hypothyroidism	0.83 (0.41, 1.66)	1.20 (0.49, 2.92)	0.28 (0.04, 1.09)
Migraines	**10.50 (4.75, 26.66)**	**4.94 (1.75, 13.92)**	**36.89 (9.30, 238.93)**
Any autoimmune disorder(s)	0.66 (0.33, 1.25)	1.02 (0.43, 2.38)	0.28 (0.06, 0.92)
Preeclampsia and/or gestational hypertension	**3.02 (1.09, 9.72)**	2.41 (0.47, 12.47)	**4.67 (1.19, 23.05)**
Number of children: 2 to 3	**2.26 (1.22, 4.29)**	**2.82 (1.22, 6.53)**	1.60 (0.62, 4.42)
Number of children: 4+	1.87 (0.62, 5.61)	2.92 (0.59, 14.41)	1.31 (0.23, 6.37)
Number of nonterm pregnancies: 1	1.16 (0.59, 2.25)	1.51 (0.62, 3.66)	0.78 (0.26, 2.20)
Number of nonterm pregnancies: 2+	1.37 (0.67, 2.82)	**2.97 (1.11, 7.93)**	0.25 (0.04, 1.05)

OR and 95% CI are from univariable logistic regression models. Boldface indicates statistical significance of $P < 0.05$.

BMI, body mass index; CA, coronary angiogram; CAD, coronary artery disease; CTA, computed tomography coronary angiogram; CI, confidence interval; CVD, cardiovascular disease; INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, MI with no obstructive coronary arteries; (M)INOCA, MINOCA or INOCA; OR, odds ratio; ref, referent.

*Any obstructive CAD: includes MI-CAD and non-MI CAD.

1.09, 9.72], $P = 0.04$); and having 2-3 children (OR 2.26 [95% CI 1.22, 4.29], $P = 0.011$).

The following risk factors, which are known to be strongly associated with obstructive CAD, were strongly and negatively associated with (M)INOCA as compared to their obstructive counterparts (OR < 0.5): current smoker (OR 0.08 [95% CI 0.02, 0.25], $P < 0.001$); former smoker (OR 0.21 [0.10, 0.41], $P < 0.001$); type 1 or type 2 diabetes (OR 0.26 [95% CI 0.13, 0.50], $P < 0.001$); obesity (OR 0.34 [95% CI 0.19, 0.58], $P < 0.001$); not partnered (OR 0.35 [95% CI 0.18, 0.67], $P = 0.002$); non-Caucasian race (OR 0.41 [95% CI 0.23, 0.71], $P = 0.002$; and dyslipidemia (OR 0.43 [95% CI 0.25, 0.71], $P = 0.001$).

Risk factors that were not significantly associated with (M)INOCA compared to any obstructive CAD were family history of CVD, depression and/or anxiety, hypothyroidism, and any autoimmune disease.

Multivariable regression models

After iterative multivariable regression models were fitted and assessed, the final model of (M)INOCA relative to any obstructive CAD included the following (Fig. 4B): age of earliest angiography (OR 0.96 [95% CI 0.90, 1.03], $P = 0.25$; diabetes (OR 0.15 [95% CI 0.05, 0.40], $P < 0.001$); depression and/or anxiety (OR 2.75 [95% CI 1.16, 6.92], $P = 0.025$; migraines (OR 6.84 [95% CI 2.56, 21.74], $P < 0.001$; current smoking history (OR 0.06 [95% CI 0.01, 0.24], $P < 0.001$; previous smoking history (OR 0.16 [95% CI 0.06, 0.42], $P < 0.001$; and preeclampsia or gestational hypertension (OR 5.85 [95% CI 1.40, 30.58], $P = 0.022$).

Discussion

This study demonstrated distinct differences in risk factor profiles of women with premature (M)INOCA—notably nontraditional CV risk factors such as migraines, preeclampsia or gestational hypertension, and depression and/or anxiety—compared to those with premature obstructive CAD, characterized mostly by traditional CV risk factors. These differences suggest different mechanisms and etiologies, underscoring a need for clinicians to collect and assess emerging nontraditional and sex-specific variables as risk factors that put patients at higher relative risk of (M)INOCA.

The results of this study support the hypothesis of possible shared vasomotor disorder mechanisms among (M)INOCA, migraines, and preeclampsia or gestational hypertension. This concept of a systemic vasomotor disorder is not new; previous studies have identified strong associations with migraines and Raynaud's syndrome in patients with vasospastic angina.[29] However, very few molecular (ie, genetic) studies of vasomotor (M)INOCA etiologies are available that could connect shared molecular mechanisms of these disorders. Multiple routes toward dysfunctional modulation of vascular tone by the endothelium have been proposed—enhanced coronary vasoconstrictive reactivity at the microvascular level, impaired

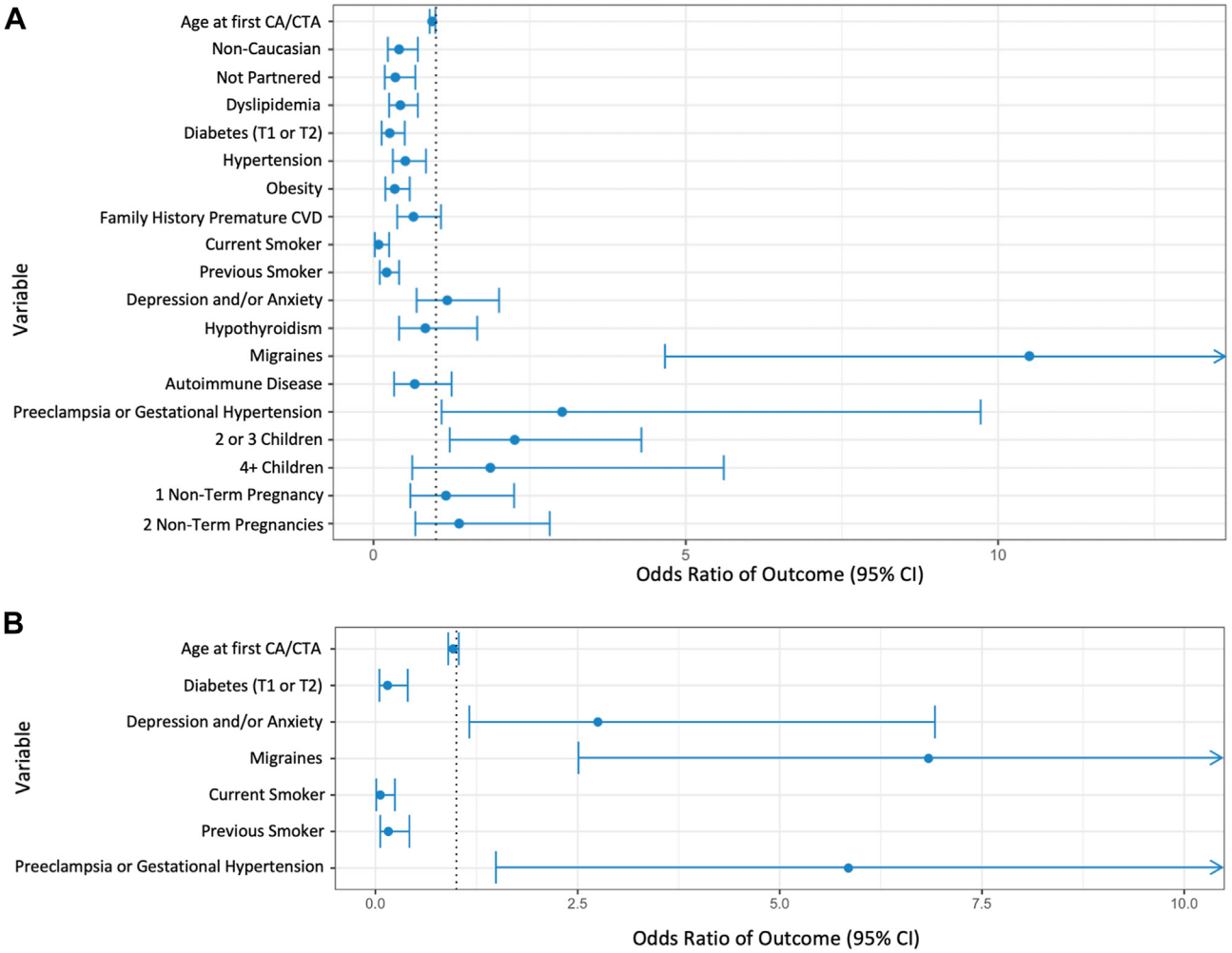

Figure 4. Forest plots of odds ratios with 95% CI for (M)INOCA compared to any obstructive CAD. (**A**) Univariable odds ratios; (**B**) multivariable (adjusted) odds ratios. CA, coronary angiogram; CI, confidence interval; CAD, coronary artery disease; CTA, computed tomography coronary angiogram; CVD, cardiovascular disease; (M)INOCA, myocardial infarction with no obstructive coronary arteries (MINOCA) or ischemia with no obstructive coronary arteries (INOCA); T1, Type 1; T2, Type 2.

endothelium-independent and -dependent vasodilatory capacity, and increased microvascular resistance due to structural factors (eg, vascular remodelling, luminal narrowing).[30] Furthermore, a sex-specific effect of high estrogen levels (relative to postmenopausal levels) may occur on subtypes of these pathologies, as estrogen promotes nitric oxide (NO) production via activation of NO synthase and subsequent endothelium-dependent vasodilation.[31] More research is required to understand the differences and shared mechanisms among cardiac vasomotor subtypes with noncardiac vasomotor etiologies (ie, migraines), and the role of sex hormones.

A noteworthy finding was the emergence of depression and/or anxiety as an independent variable in the adjusted multivariable model, as it was not significant in the univariable models for (M)INOCA. Depression and anxiety are highly comorbid conditions with each other, and they occur in women with IHD more frequently than in men with IHD.[32] A persistent depressive state has been associated with abnormal vascular reactivity, predominantly through autonomic dysfunction and cumulative effects over time from chronic low-grade inflammation.[33] Depression and anxiety can have acute and chronic effects on the dysregulation of vasovagal tone through persistent activation of the hypothalamic-pituitary-adrenal axis, which exhibits sex differences in vasoconstrictive responsiveness.[34] Thus, prolonged activation may further exacerbate risk of (M)INOCA in women with a higher predisposition toward vasomotor syndromes. Altogether, these findings support a complex and bidirectional mechanism of depression and/or anxiety contributing to (M)INOCA risk.

Pregnancy has lifelong impacts on women's physiology, with numerous studies demonstrating pregnancy's long-term benefits on immune[35] and CV health.[36] A proposed explanation for this link is improved endothelial function resulting in greater bioavailable NO during pregnancy that persists postpartum.[37,38] In the current study, having 2-3 children was associated with increased odds of (M)INOCA, which may also be interpreted as having 2-3 children being associated with a lower risk of CAD. This relationship has been reported previously as a J-shaped curve, with having 2-3 children being associated with fewer CV events than having 0-1 or 4+ children.[39] Because our findings relate to (M)INOCA relative

to CAD, this question needs to be examined in future studies comparing women with CAD or (M)INOCA to women with no IHD.

The prevalences of traditional CV risk factors, dyslipidemia, diabetes, and smoking status in our (M)INOCA cohort are similar to those in the general Canadian population of 45%, 11%, and 10%, respectively.[40-42] This similarity differs from migraines, which were observed to occur over 4 times as frequently in the (M)INOCA cohort (36%), compared to the Canadian population (8.3%).[43] Focusing on traditional CV risk factors allows for reasonable prediction of possible premature obstructive CAD but not premature (M)INOCA, as most (M)INOCA patients did not have these traditional risk factors.

Limitations of this study include its small sample size (particularly of MINOCA patients), the lack of racial and/or ethnic diversity, and the omission of other sex-specific variables emerging as CV risk factors, owing to the absence of systematic collection in either or both cohorts, such as premature menopause (at age < 45 years), endometriosis, and polycystic ovarian syndrome. The extent to which the results from this study would apply to non-Caucasian populations is unclear; for example, several studies have shown significantly higher prevalence of vasospasm by provocative testing in people of Japanese,[44] Taiwanese,[45] and South Korean[46] descent, as compared to Caucasians.[22] However, the risk factor profiles of the young women within these populations are not clear.

Conclusions

Our study on risk factors associated with vasomotor etiologies of premature (M)INOCA compared to those associated with premature obstructive CAD provides further evidence that these entities demonstrate distinct risk factor profiles in young women. Specifically, nontraditional risk factors, such as migraines, preeclampsia or gestational hypertension, and depression and/or anxiety increase the risk of (M)INOCA and should be documented reliably in all patients presenting with possible IHD. Future studies with larger sample sizes, both sexes, and systematic collection of nontraditional risk factors are needed to improve our understanding of the mechanisms of vasomotor pathology in these premature-onset populations.

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Ethics Statement

This collaborative study was approved under the University of British Columbia Clinical Research Ethics Board application #H22-01671.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective analysis of de-identified data of 2 cohorts; therefore, the University of British Columbia Clinical Research Ethics Board did not require consent from the patients.

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Disclosures

The authors have no conflicts of interest to disclose.

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Given her role as Associate Editor, Karin Humphries had no involvement in the peer review of this article and has no access to information regarding its peer review.

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