

Original Article

Coronary artery disease in the young in the US population-based cohort

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Abstract: Background: Although most prevalent in the elderly, coronary artery disease (CAD) also affects younger adults. However, CAD in young adults is not as well characterized. Objective: To explore factors associated with CAD in young patients. Methods: We investigated the prevalence and baseline characteristics of young patients with CAD using the National Health and Nutrition Examination Survey (NHANES) survey between 1999 and 2016. The primary outcome was a reported history of CAD at age <55 years old, defined based on the subject's response to survey questions 'Have you ever been told by a physician that you had coronary artery disease?' and 'How old were you when were told you had coronary heart disease?'. Multivariable logistic regression models were used to assess factors associated with CAD in young patients. Results: Of 42,038 NHANES participants, 707 (1.7%) reported CAD at young age. Young patients with CAD were more likely to be male, non-whites, cigarette smokers, recreational drug users, had a family history of CAD, compared to young patients without CAD (all *p*-values <0.05). In multivariable logistic regression models, diabetes (OR: 3.94; 95% CI: 1.32-11.8; *P*=0.01), cigarette smoking (OR: 2.86; 95% CI: 1.52-5.53; *P*=0.001), alcohol consumption (OR: 1.17; 95% CI: 1.04-1.35; *P*=0.01) and cocaine use (OR: 4.48; 95% CI: 1.33-15.1; *P*=0.01) were independently associated with CAD in young patients. Conclusion: CAD in young patients may be influenced by lifestyle factors such as alcohol consumption or cocaine use, as well as conventional risk factors such as smoking or diabetes.

Keywords: Coronary artery disease, CAD, CAD in young patients, NHANES, lifestyle factors

Introduction

Though coronary artery disease (CAD) in the young is increasingly recognized, its true prevalence is unknown. Studies show that conventional risk factors such as smoking, diabetes, hypertension, and family history of CAD seem to be as important in the young patients as they are in older patients with CAD [1]. Some studies have shown that family history of CAD is also independently associated with CAD in young patients [2], while a recent study reported that lifestyle risk factors (e.g., smoking, sleep duration, alcohol consumption) were also associated with young patients with CAD [1, 3, 4]. Studies have also shown that the prevalence of

smoking in young patients with CAD is higher than older patients with CAD and smoking seems to be the most common risk factor in young patients with CAD [5, 6]. Other conditions including hypothyroidism, rheumatoid arthritis, liver disease, and HIV have been reported to be associated with accelerated atherosclerosis as well as incidence of CAD in young patients. Majority of current data is based on single-center studies which may not be representative of the overall United States (US) population. We therefore sought to investigate factors associated with CAD in young patients in a nationally representative cohort using the NHANES survey between 1999 and 2016.

Methods

Study population

The NHANES survey, a nationally representative sample of the US population of general health, household interviews, nutrition, lifestyle factors and environmental exposures, was conducted by the CDC along with the National Center for Health Statistics (NCHS) (<https://www.cdc.gov/nchs/nhanes/>). Data from NHANES cohorts from 1999-2016 were extracted to construct the study population. The NHANES study was reviewed and approved by the National Center for Health Statistics Research Ethics Review Board and all participants provided signed consent for participation. Patients were not involved in this analysis.

Variables

We assessed demographic factors including age, gender, race, marital status, family income, education, comorbidities (e.g., hypertension, hyperlipidemia, diabetes), and lifestyle variables (e.g., alcohol consumption, cigarette smoking, recreational drug use, sleep duration) and compared differences amongst those age <55 years with or without CAD. Individuals who age > 55 years old were excluded. Missing variables were also excluded.

Outcomes

Our primary outcome was prevalence of CAD in young adults, defined based on the subject's response as 'yes' to the survey question 'Have you ever been told by a physician that you had coronary artery disease?' and a response of age less than 55 years to the survey question 'How old were you when were told you had coronary heart disease?'. Daily dietary caffeine intake was obtained from the Total Nutrient Intakes interview. Alcohol consumption measurement was obtained from self-reported average number of alcoholic drinks per week over the previous 12 months. Recreational drug uses were defined based on the subject's response as yes to survey questions "Have you ever used cocaine, heroin, or methamphetamine?".

Statistical analysis

Mean \pm standard deviation was reported for continuous variables and frequency with per-

centages for categorical variables. We then used multivariable logistic regression models to assess the independent association between various risk factors and CAD in young patients. Variables adjusted for included age, gender, race, family history of CAD, BMI, marital status, educational level, current cigarette smoking, alcohol consumption, sleeping hours, caffeine use, substance use, systolic and diastolic blood pressure. All analyses were performed using Stata version 14.2 and R 3.4.0. All *p* values were 2-sided and statistical significance was determined at $P < 0.05$.

Results

Of 42,038 NHANES participants, 2,001 (4.8%) had CAD. Of those 2,001 patients, 707 (35.3%) reported CAD at young age. **Table 1** demonstrates the baseline characteristics of young patients with CAD ($n=707$) in comparison to those without CAD and age ≤ 55 years ($n=29,809$). Young patients with CAD were more likely to be male, black, had family history of CAD compared with those without CAD aged ≤ 55 years. (all *p*-values < 0.05) Young patients with CAD also had a higher prevalence of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD) and liver disease (all *p*-values < 0.05). (all *p*-values < 0.05). Young patients with CAD were more likely to be cigarette smokers, cocaine/methamphetamine users, compared to those without CAD at age ≤ 55 years (all *p*-values < 0.05) (**Table 1**).

Traditional CAD risk factors in young patients with CAD

Among traditional CAD risk factors, BMI (OR: 1.04; 95% CI: 1.02-1.06; $P < 0.0001$), family history of CAD (OR: 3.26; 95% CI: 2.30-4.61; $P = 0.0006$), cigarette smoking (OR: 4.23; 95% CI: 4.00-4.48; $P < 0.0001$), diabetes (OR: 4.99; 95% CI: 3.60-6.92; $P < 0.0001$), hypertension (OR: 5.03; 95% CI: 2.78-9.11; $P < 0.0001$), and hyperlipidemia (OR: 12.3; 95% CI: 8.40-18.04; $P < 0.001$) were associated with CAD at young age in univariate analyses (**Table 2**). After multivariable adjustment, cigarette smoking (OR: 2.86; 95% CI: 1.52-5.53; $P = 0.001$) and diabetes (OR: 3.94; 95% CI: 1.32-11.8; $P = 0.01$) remained independently associated with CAD in young patients (**Table 2**).

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Table 1. Demographic and baseline characteristics among young patients with coronary artery disease

	Young patients without CAD (n=29,809)	Young Patients with CAD (n=707)	p-value
Age, years (mean ± SD)	36.97 ± 10.33	47.2 ± 7.6	<0.0001
Male gender	47%	62%	<0.0001
White	43%	49%	0.001
Family history of CAD	7.9%	20%	<0.0001
High school graduate/GED or equivalent	76%	62%	<0.0001
Monthly Family income <\$800	56.5%	56.8%	0.87
Monthly Family income > \$8,400	5.1%	7.8%	0.001
Hypertension	13.4%	62%	<0.0001
Cigarette smoking	26%	36%	<0.0001
Hyperlipidemia	8.2%	57%	<0.0001
Diabetes mellitus	5.3%	23%	<0.0001
Thyroid disorder	4.8%	7%	0.007
COPD	8.6%	10.2%	0.13
BMI (mean ± SD)	28.78 ± 7.03	30.71 ± 7.40	<0.0001
SBP (mean ± SD)	118.36 ± 14.98	125.41 ± 19.71	<0.0001
DBP (mean ± SD)	63.8 ± 15.6	70.1 ± 14.6	<0.0001
Sleep hours (mean ± SD) (hours)	6.86 ± 3.13	6.94 ± 7.75	0.54
Alcohol use (mean ± SD) (drinks per week)	3.42 ± 2.22	3.1 ± 2	0.68
Caffeine use (mean ± SD) (mg/day)	148.83 ± 206.86	178.21 ± 248.24	0.0002
Cocaine use	0.1%	7.6%	<0.0001
Heroin use	0.09%	1.5%	<0.0001
Methamphetamine use	0.08%	3.5%	<0.0001

Lifestyle risk factors in young patients with CAD

Among lifestyle risk factors, sleep hours (OR: 0.97; 95% CI: 0.96-0.98; P<0.0001), cocaine use (OR: 1.06; 95% CI: 1.03-1.51; P=0.005), heroin use (OR: 0.79; 95% CI: 0.69-0.90; P=0.0006), and methamphetamine use (OR: 1.24; 95% CI: 1.07-1.46; P=0.005) were associated with CAD in young patients in univariate analyses (**Table 3**). After multivariable adjustment, alcohol consumption (OR: 1.17; 95% CI: 1.04-1.35; P=0.01) and cocaine use (OR: 4.48; 95% CI: 1.33-15.1; P=0.01) remained independently associated with CAD in young patients (**Table 3**).

Discussion

To the best of our knowledge, this is the first analysis using a large nationally representative dataset to identify the baseline characteristics of young patients with CAD in the US general population. There are two main findings from the present study. First, after adjustment for

confounders, we found that traditional risk factors such as diabetes and smoking were independently associated with CAD in young patients. Second, among lifestyle factors, we found that cocaine use and alcohol consumption were independently associated with CAD in young patients.

Traditional CAD risk factors in young patients with CAD

In the present study, we found that only cigarette smoking and diabetes were independently associated with CAD in young patients in US. Diabetes has long been considered among the most important risk factors for CAD in both older adults and young patients with CAD. The results of our study were consistent with previous studies from China which showed that diabetes mellitus, cigarette smoking, and alcohol consumption were significantly related to CAD in patients aged ≤40 [7]. Similarly, a study in Pakistan reported that cigarette smoking, and diabetes mellitus were the main risk factors of CAD in patients below 45 years of age [8].

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Table 2. Multivariate logistic regression analyses for traditional risk factors in Young Patients with Coronary Artery Disease

Variable	Adjusted OR [95% CI]	Adjusted P value
BMI		
No adjustment	1.04 (1.02-1.06)	<0.0001
Multivariable adjusted	0.98 (0.89-1.08)	0.70
Family history of CAD		
No adjustment	3.26 (2.30-4.61)	0.0006
Multivariable adjusted	1.52 (0.29-7.90)	0.62
Cigarette smoking		
No adjustment	4.23 (4.00-4.48)	<0.0001
Multivariable adjusted	2.86 (1.52-5.53)	0.001
Diabetes		
No adjustment	4.99 (3.60-6.92)	<0.0001
Multivariable adjusted	3.94 (1.32-11.78)	0.01
Hypertension		
No adjustment	5.03 (2.78-9.11)	<0.0001
Multivariable adjusted	1.50 (0.26-8.70)	0.65
Hyperlipidemia		
No adjustment	12.31 (8.40-18.04)	<0.0001
Multivariable adjusted	1.38 (0.40-4.76)	0.62

Multivariable logistic regression models adjusted for age, sex, race, family history, BMI, marital status, educational level, current cigarette smoking, alcohol consumption, sleep hours, caffeine use, recreational drug use, systolic and diastolic blood pressure.

Several studies in India [9], Indonesia [10], Turkey [11], Japan [12], Egypt [13] have also shown cigarette smoking as one of the most important risk factors among younger patients with CAD. Overwhelming evidence suggests that smoking is one of the strongest risk factors for young patients with CAD and accelerates atherosclerosis [14, 15]. In the Framingham Heart Study, compared to nonsmokers, the relative risk for CAD was about three times higher in smokers age 35 to 44. Cigarette smoking has also been shown to be strongly associated with “atherogenic” lipoprotein cholesterol profiles in young adults [16, 17]. Surprisingly, after adjustment for confounders, family history of CAD was not independently associated with CAD in young patients, suggesting lifestyle factors may have more pronounced effect than genetics. It is also likely that a family history of CAD could be explained by familial clustering of unhealthy lifestyle habits (e.g., smoking, low fruit and vegetable intake, high salt diet, sedentary behaviors, or physical inactivity), leading to

increase the risk of CAD in young patients. Gene-environment interactions especially in the presence of an unhealthy family lifestyle could amplify this effect. Early identification of risk factors and lifestyle interventions at an earlier age may be beneficial to mitigate this risk.

Lifestyle risk factors in young patients with CAD

Lifestyle is known to be one of the most important factors associated with CAD in young patients. Individuals may adopt unhealthy habits from friends in school/college, neighbors in childhood, or work environment in early career. Although data on alcohol consumption and CAD is conflicting, alcohol consumption is a leading risk factor for premature death and all-cause mortality in young males [18, 19]. Several studies have found that alcohol consumption may decrease risk of CAD [20, 21] but those studies were perhaps confounded by duration of consumption, drinking patterns (e.g., binge drinking) and type of alcohol [22]. In CARDIA study, the investigators found a pro-atherogenic effect of alcohol in young adults which may counterbalance other possible benefits of alcohol consumption [22]. In fact, genetics may play an important role in alcohol metabolism (e.g., APOE allele or beta fibrinogen genes), resulting in population-level variability in health benefits or risks from alcohol consumption [23, 24]. It is also possible that the association seen with alcohol consumption is confounded by presence of other concomitant risk factors in those with alcohol use.

Strong evidence suggested that cocaine use is associated with CAD in young patients [25, 26]. A small study of CAD patients with age ≤50 years suggested the proatherosclerotic effects of cocaine in humans [27]. Cocaine use in young patients has also been shown to accelerate atherosclerosis [27]. The underlying mechanism for the association between cocaine use and CAD in young adults is not well understood but is likely due to endothelial cell dysfunction [28].

Study limitations

Our study has certain limitations. First, the study design lends itself to inherent confound-

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Table 3. Multivariate logistic regression analyses for lifestyle risk factors in Young Patients with Coronary Artery Disease

Variable	Adjusted OR [95% CI]	Adjusted P value
Sleep hours		
No adjustment	0.97 (0.96-0.98)	<0.0001
Multivariable adjusted	0.99 (0.82-1.19)	0.93
Alcohol use		
No adjustment	0.99 (0.99-1.00)	0.33
Multivariable adjusted	1.17 (1.04-1.35)	0.01
Caffeine use		
No adjustment	0.99 (0.99-1.00)	0.46
Multivariable adjusted	1.00 (0.99-1.00)	0.40
Cocaine use		
No adjustment	1.06 (0.73-1.51)	0.005
Multivariable adjusted	4.48 (1.33-15.1)	0.01
Heroin use		
No adjustment	0.79 (0.69-0.90)	0.0006
Multivariable adjusted	1.32 (0.38-4.69)	0.65
Methamphetamine use		
No adjustment	1.24 (1.07-1.46)	0.005
Multivariable adjusted	0.78 (0.38-1.57)	0.49

Multivariable logistic regression models adjusted for age, sex, race, family history, BMI, marital status, educational level, current cigarette smoking, alcohol consumption, sleeping hours, caffeine use, recreational drug use, systolic and diastolic blood pressure.

ing and selection biases due to the cross-sectional design of the NHANES survey. We did not control for potential confounders such as psychological stress, genetics (e.g., polymorphisms in 9p21 loci), Lp(a) levels, congenital anomalies of the coronary arteries, patent foramen ovale (paradoxical embolism), myocardial bridging, radiation therapy for chest tumors, and chest trauma as these variables were not available. In addition, we could not assess potential baseline characteristics such as chronic inflammatory autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis), polycystic ovarian syndrome, preeclampsia, gestational diabetes, or estrogen use. Lastly, given cross sectional design, our results do not imply causation.

Conclusions

CAD in young patients in US may be influenced by lifestyle factors such as alcohol consumption or cocaine use, as well as traditional risk

factors such as smoking or diabetes. Public health measures targeting these at-risk populations may reduce burden of CAD in young patients. Smoking cessation, lifestyle interventions to prevent diabetes, and behavior modification to reduce cocaine use among young individuals may be effective approaches in primary CAD prevention in young adults.

Disclosure of conflict of interest

None.

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