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Risk Estimates for Atherosclerotic Cardiovascular Disease in Adults with Congenital Heart Disease

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Abstract

The adult with congenital heart disease (CHD) is at risk of developing atherosclerotic cardiovascular disease (ASCVD). We performed a cross-sectional study to describe established ASCVD risk factors and estimate 10-year and lifetime risk of ASCVD in adults over age 18 with CHD of moderate or great complexity using three validated risk assessment tools—the Framingham Study Cardiovascular Disease Risk Assessment, the Reynolds Risk Score, and the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator. We obtained extensive clinical and survey data on 178 enrolled patients, with average age 37.1 ± 12.6 years, 51% men. At least one modifiable ASCVD risk factor was present in 70%; the two most common were overweight/obesity (53%) and systemic hypertension (24%). Laboratory data was available in 103 of the 178 patients. Abnormal levels of glycated hemoglobin, high-sensitivity C-reactive protein, and high-density lipoprotein (HDL) were each found in around 30% of patients. The 10-year ASCVD predicted risk using all three tools was relatively low (i.e., at least 90% of patients <10% risk), yet

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the median estimated lifetime risk was 36%. In conclusion, ASCVD risk factors are prevalent in adults with CHD. The risk estimation tools suggest that this population is particularly vulnerable to ASCVD with aging and should undergo guideline-based screening and management of modifiable risk factors.

Keywords

Adult congenital heart disease; cardiovascular disease risk; adult co-morbidities

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality in adults in the United States.¹ Risk estimates for atherosclerotic CVD (ASCVD) are an important way to anticipate the future burden of ASCVD and to motivate adherence to lifestyle changes and therapies.² The Framingham Risk Assessment is a simple and well-validated tool for identifying persons at risk for ASCVD.³ The Reynolds Risk Score adds additional biomarkers to the traditional risk factors of age, sex, hypertension, smoking, diabetes, and lipid panel in the Framingham Risk Assessment.^{4,5} More recently, the American College of Cardiology has advocated the use of the Atherosclerotic Cardiovascular Disease Risk Estimator in its recommendation for statin initiation.⁶ All of these risk models for ASCVD have been used in the general population to assess ASCVD risk but have not been applied to the congenital heart disease (CHD) population. Adults with CHD represent an emerging population that may be at increased risk for developing ASCVD.^{7,8} Physical inactivity, obesity, and diabetes may be at least as prevalent in CHD patients as the general population.⁹ Additionally, certain types of CHD and/or prior surgical repair have been associated with increased risk of ASCVD.^{7,8} Risk factors for ASCVD in the CHD population have not been well documented. Therefore, the aim of this study is to describe predicted ASCVD risk in adults with CHD of moderate or great complexity¹⁰, through established risk estimate tools: the Framingham Risk Assessment, Reynolds Risk Score and ASCVD Risk Estimator.

Methods

We conducted an observational, cross sectional study of adults older than 18 years of age who had repaired CHD of moderate or great complexity.¹⁰ Patients who were pregnant, cyanotic, had undergone surgery within the last 6 months, or carried the diagnosis of Eisenmenger syndrome were excluded. All consecutive patients meeting inclusion criteria were approached for possible enrollment in the adult CHD (ACHD) clinic during a routine visit between April 2014 and August 2015. Eleven patients who met study criteria were not approached for enrollment because they left the clinic prior to recruitment. The study had four components: physical examination, an online-survey, a medical record review, and laboratory studies. Recruitment continued until a minimum of 100 patients completed all aspects of the study. Written informed consent was obtained at the time of enrollment. The study was approved by the Stanford University Institutional Review Board.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Stanford Center for Clinical Informatics. REDCap (Research Electronic Data

Capture)¹¹ is a web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Participants underwent measurements of height, weight, waist circumference (at the level of the umbilicus) and blood pressure. Blood pressure was recorded as the average of 3 measurements taken 5 minutes apart during rest and in the supine position. The average of the three blood pressures was then calculated. Body mass index (BMI) was calculated based on height and weight. A BMI less than 18.5 was considered underweight, a BMI between 18.5 and 24.9 was considered normal, a BMI between 25.0 and 29.9 was defined as overweight and a BMI ≥ 30 was considered obese. A normal waist circumference was ≤ 35 inches for women and ≤ 40 inches for men.¹² Normal systolic blood pressure was defined as <140 mmHg.

Participants completed an online ASCVD risk factor survey. The following self-reported data were collected: history of systemic hypertension, diabetes, dyslipidemia and known ASCVD. Patients were also asked about smoking/tobacco use, physical activity and family history of first-degree family member with early coronary heart disease (≤ 60 years of age). The survey also included questions about cardiac symptoms, perceived stress, race, and ethnicity. Medical records were reviewed for the following data: date of birth, sex, type of insurance and baseline CHD. In addition current medications and their indication for use was reviewed to distinguish the difference between medications utilized for arrhythmias and heart failure from those specifically used for the treatment of hypertension which was necessary for the risk factor models.

Phlebotomy was performed in the fasting state at local Quest Diagnostics® laboratories. Laboratory fees were paid directly by the study. Blood tests included a lipid panel, glucose, glycated hemoglobin (HbA1c) and high-sensitivity C-reactive protein (hs-CRP). Patients who failed to complete the laboratory studies within one month after physical examination received a follow-up letter reminding them of the need for testing. A phone call was made to the patient at three months for a final reminder.

Elevated fasting glucose was defined as ≥ 100 mg/dL. HbA1c between 5.7% and 6.4% was indicative of pre-diabetes and HbA1c $\geq 6.5\%$ of diabetes. Normal hs-CRP was defined as <3.0 mg/L. An elevated cholesterol was defined as a total cholesterol ≥ 200 mg/dL and a low HDL level as <40 mg/dL. An elevated low-density lipoprotein (LDL) was defined per ACC/AHA guidelines⁶ as a primary elevation ≥ 190 mg/dL or an LDL of >70 mg/dL with the presence of diabetes in a subject 40–75 years of age, and patients with a ASCVD predicted risk $>7.5\%$ with an LDL >70 mg/dL. Triglyceride levels were defined as ≥ 200 mg/dL. The risk for metabolic syndrome as defined by the guidelines set forth by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) and the American Heart Association (AHA)^{12,13} was also assessed with laboratory studies.

Based on identified ASCVD risk factors and laboratory testing results, ASCVD risk was estimated utilizing three different risk calculators: the Reynolds Risk Score⁴ (validated in the age 45+ population), the Framingham Study Cardiovascular Disease (10-year) Risk Assessment³ (validated in the age 30+ population) and the ASCVD Risk Estimator for both 10-year and lifetime ASCVD risk⁶ (validated in the age 40–79 and age 20–60 populations, respectively). The traditional Framingham risk assessment only evaluated risk for coronary related death and myocardial infarction over 10 years. The ASCVD risk estimator expands on the Framingham risk score by including the development of death related to heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke.¹⁴ The Reynolds Risk Score was developed and validated in a population of American women followed over 10 years for myocardial infarction, stroke, angioplasty, coronary artery bypass surgery, and death related to heart disease.⁴

Demographics, binary ASCVD risk factors, and categorizations of laboratory results were summarized by CHD complexity, and differences between complexity groups were assessed using Pearson's chi-square test or Fisher's exact test for categorical variables and t-tests for patient age. Distributions of biomarkers by CHD complexity were examined graphically. ASCVD risk scores were calculated using the patient's actual age if it was within the age range for which the tool had been validated, and if the patient was younger than the validated age range, the boundary age closer to his/her actual age was used. For example, a 25 year-old would be considered 25 by the ASCVD lifetime tool, 30 by the Framingham tool, 40 by the ASCVD 10-year tool, and 45 by the Reynolds tool. We felt this approach to be reasonable, as estimated age-related risk does not begin to increase until the patient reaches a threshold that is above the minimum age in each risk score formula. Risk scores were not calculated for patients who exceeded validated age ranges, as the age-associated increase in risk score is unknown and would likely be different from the increase in predicted risk for the validated age ranges. Distributions of 10-year ASCVD risk scores for all patients and for patients within the tools' validated age ranges were examined graphically. Patients without full information for risk score calculations were excluded from regression analyses. A two-sided p-value of <0.05 indicated statistical significance. All analyses were performed using SPSS software version 23 (Chicago, IL) and R version 3.3.

Results

A total of 178/208 (88%) patients approached for study participation agreed to enrollment. There were no significant differences in demographic or clinical characteristics between patients who agreed to participate and those who did not (results not shown). Characteristics of the study population can be found in Table 1. Among the enrolled patients, the average age was 37.1±12.6 years; 51% were male. Slightly more than half (57%) had CHD of moderate complexity, while the remainder had CHD of great complexity. The most common CHD diagnosis was tetralogy of Fallot (26%), followed by transposition of the great arteries (20%) and Fontan operation in patients with single ventricle physiology (15%). Of the 172 patients who reported their New York Heart Association (NYHA) functional classification, 45%, 41%, 10% and 3% belonged to functional classes I–IV, respectively. Cardiac medications were currently used by 105 (59%) of the patients, with the most common ones being ACE inhibitor/angiotension receptor blocker (30%, n=53), beta blocker (21%, n=37)

and diuretic (21%, n=37). Aspirin was utilized by 24% (43) of patients, and 18% (32) of patients were on warfarin or novel oral anti-coagulant. A statin was used by 11% (20) and medications for the management of type 2 diabetes were used by 5% (8) of patients.

ASCVD risk factors by are presented in Table 2. At least one modifiable ASCVD risk factor was noted in 70% of patients. Excess adiposity was the most common risk factor: 53% of patients were overweight and 21% were obese. Systemic hypertension was reported by 17%, 5% had a known history of diabetes and a history of dyslipidemia was reported by 20% of patients. Smoking was uncommon (2%), although 18% of patients stated they had previously smoked. Most (87%) patients engaged in some form of physical activity, with 29% reporting exercising at least 1–2 days per week, 37% reporting exercising 3–4 days per week and 21% reported exercising 5–7 days per week.

Of the patients enrolled in this study, 103/178 (58%) completed the fasting laboratory studies, which was a necessary component of all risk estimation tools utilized. There were no significant differences in demographic or clinical characteristics between patients who completed their fasting laboratory studies and those who did not (Tables 1 and 2). At least one abnormal laboratory result was found in 71 of these 103 (69%) of patients. Elevated hs-CRP and low HDL (both noted in 28% of patients) and elevated HbA1c were the most commonly noted abnormal laboratory findings (Figure 1a and 1b). The median HbA1c was 5.4% (IQR 5.3% to 5.7%). Pre-diabetes was noted in 29/103 (28%) of patients and diabetes was present in two patients. Of the patients noted to have an elevated HbA1c, only 2 had been previously diagnosed with diabetes, neither of whom was on pharmacological treatment. Metabolic syndrome was identified in 8% of patients, and 22% were one risk factor away from meeting criteria for metabolic syndrome.

At least one abnormal lipid level was noted in 44/103 (43%) of patients (Figure 1a). Four patients had a total cholesterol over 250mg/dL (254, 276, 299 and 306mg/dL). HDL was noted to be low in 29/103 (28%), 10 of whom had a HDL less than 30mg/dL. An elevated LDL was noted in 6/103 (6%) of patients. Two patients had a LDL > 190 mg/dL while the other 4 patients met the ACC/AHA guideline for abnormal LDL. Triglycerides were elevated in 11/103 (11%) of patients, with 1 subject having a triglyceride of 510mg/dL. Of the patients with an indication for statin therapy, only 45% of those patients were on one.

The distributions of estimated 10-year ASCVD risk scores utilizing the Framingham Risk Assessment, Reynolds Risk Score and ASCVD Risk Estimator for patients in validated age ranges and for all patients who completed the fasting laboratory studies are shown in Figure 2a and 2b; respective medians and interquartile ranges (IQR) of estimated 10-year ASCVD risk scores were 1.9% (1.2, 4.2); 1.0% (1.0, 2.0); and 0.9% (0.5, 1.9) respectively. The distribution of all estimated risk scores are presented in Supplemental Figure S1. The median estimated ASCVD lifetime risk scores for these patients was 36% (IQR 8, 46).

Discussion

Risk factors for ASCVD were common in our cohort of adults with CHD of moderate or great complexity, with 70% having at least one modifiable risk factor. Systemic hypertension

and being overweight or obese were the most prevalent risk factors in this cohort. Although the percent overweight or obese patients in our cohort (53%) was less than in the general U.S. population (69%)¹⁵, it is of concern and weight management should be a focus for prevention and intervention. ASCVD may be the next threat to this patient population and will likely have far greater impact than the general population due to less than ideal hemodynamics and multi-organ dysfunction related to underlying CHD.

Although Moons et al. described a similar prevalence of risk factors in adults with CHD⁹, this investigation adds to that study by including prospectively examination of fasting glucose, HbA1c, lipid panel and hs-CRP and estimating future ASCVD risk. Nearly two-thirds of patients in our study had at least one abnormal laboratory value, and less than half of these had been previously diagnosed. Thirty percent of patients had an abnormal HbA1c diagnostic and met criteria for pre-diabetes or diabetes. Abnormal glucose metabolism has been noted in CHD patients as compared to healthy controls in prior studies.^{16,17} Given the link between weight and diabetes and the rates of being overweight and obese in our cohort it is reasonable to anticipate that our patients will be part of the rapidly growing population of adults with diabetes in the U.S. This may have important implications as abnormal glucose metabolism has been associated with increased morbidity and mortality in ACHD patients.¹⁸

Nearly half (44%) of the 103 patients in this study had at least one abnormal lipid level. Hyperlipidemia has been noted in surgically corrected ACHD patients but lower cholesterol is often seen in palliated or unrepaired CHD patients who remain cyanotic.^{19,20} Almost 10% of patients in this series met criteria for metabolic syndrome^{12,13}, and others have reported their prevalence of metabolic syndrome to be 1.5 times higher in ACHD patients than in health controls.²¹ Based upon these findings, it appears prudent to consider at least guideline-based screening and management of ASCVD risk factors in the CHD population.

One Fontan patient (32 years old) in our study was newly diagnosed with hyperlipidemia during this study. He had no other risk factors including the absence of obesity (normal BMI) and no family history of CAD or hyperlipidemia. However, he did have an abnormal hemoglobin A1c of 5.7%. His lipid panel included a cholesterol of 306 mg/dL and triglyceride of 510 mg/dL. He was not on a statin at the time of the enrollment. This case illustrates the unrecognized ASCVD risk factors in patients with CHD of great complexity.

Twenty-eight percent of our cohort had hs-CRP greater than 3mg/L, which confers an increased predicted risk beyond the traditional Framingham Risk Assessment factors for ASCVD.¹⁴ CRP has been used to reclassify intermediate risk patients as high risk and permit more aggressive risk reduction therapies. The prevalence of elevated CRP level is at least 20 to 25% among intermediate risk persons.²² Hs-CRP has been correlated with other biomarkers associated with heart failure and acute coronary syndrome in ACHD patients.²³ The results in our cohort suggest a high prevalence of elevated CRP and warrant further study as a risk factor for ASCVD in this patient population.

The addition of hs-CRP and other biomarkers may be important for risk stratifying this patient population. Therefore, we used the Reynolds tool, which incorporates hs-CRP, in

addition to more traditional risk estimators, to describe ASCVD risk in this population.^{14,24} These additions in Reynolds and ASCVD may account for the differences seen in risk estimate. Predicted 10-year risk was greater than 10% in 11%, 2% and 4% of our cohort according to the Framingham Risk Assessment, Reynolds Risk Score, and ASCVD Risk Estimator, respectively. Approximately 67% had a predicted lifetime ASCVD risk of 25–50%. Patients with moderate complexity had a higher unadjusted and age-adjusted risk for ASCVD than great complexity CHD based upon both a 10-year and lifetime estimate. This difference may be related in part to the fact that patients with coarctation, who were among the most common diagnostic groups in our moderate complexity cohort, are more often male and have a higher prevalence of residual hypertension. Additionally, there is a higher prevalence of coronary artery disease in coarctation patients.²⁵

By identifying individuals at elevated risk for ASCVD, we can move to modifying their risk of developing ASCVD over time. Unfortunately, these modifiable risk factors have taken a back seat to the management of their residual CHD lesions. Therefore, it is important for providers to discuss dietary patterns, physical activity, obesity, dyslipidemia, diabetes and tobacco use. Screening for ASCVD risk factors should occur on a regular basis with the initiation of therapies based upon guidelines.⁸

Limitations of this study include the single center design with a high percentage of highly educated, non-Hispanic white patients who had private insurance. Given this, the results might not be generalizable to the ACHD population at large. In addition, the center with tertiary referrals for complex CHD cases may bias towards more comorbidities. Self-reporting may have resulted in underreporting of ASCVD risk factors. Many statistical tests were performed with no adjustment for multiple testing. Another limitation involves the estimation of risk based upon Framingham Risk Assessment, Reynolds Risk Score and ASCVD Risk Estimator. All tools were derived from an older population ages 40 to 79 years with no history of CHD disease. When the risk scores were calculated for the patients within the actual age range, the ASCVD risk was even higher suggesting that these risk scores may underestimate the risk of ASCVD in this younger population. Additionally, these risk scores do not factor in type of CHD or surgical repair, which may place an increased risk in some individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Laslett LJ, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, Wilson SR, Poe C, Hart M. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol*. 2012; 60:S1–49. [PubMed: 23257320]
2. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation*. 2010; 121:1768–1777. [PubMed: 20404268]
3. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97:1837–1847. [PubMed: 9603539]
4. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007; 297:611–619. [PubMed: 17299196]
5. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008; 118:2243–2251. [PubMed: 18997194]
6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 63:2889–2934. [PubMed: 24239923]
7. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J, American Heart Association Expert Panel on P, Prevention S, American Heart Association Council on Cardiovascular Disease in the Y, American Heart Association Council on E, Prevention, American Heart Association Council on Nutrition PA, Metabolism, American Heart Association Council on High Blood Pressure R, American Heart Association Council on Cardiovascular N, American Heart Association Council on the Kidney in Heart D, Interdisciplinary Working Group on Quality of C, Outcomes R. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006; 114:2710–2738. [PubMed: 17130340]
8. Lui GK, Fernandes S, McElhinney DB. Management of cardiovascular risk factors in adults with congenital heart disease. *J Am Heart Assoc*. 2014; 3:e001076. [PubMed: 25359401]
9. Moons P, Van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. *European journal of cardiovascular prevention and rehabilitation*. 2006; 13:612–616. [PubMed: 16874153]
10. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008; 52:e143–263. [PubMed: 19038677]

11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009; 42:377–381. [PubMed: 18929686]
12. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F, American Heart A, National Heart L, Blood I. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112:2735–2752. [PubMed: 16157765]
13. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106:3143–3421. [PubMed: 12485966]
14. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O’Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 63:2935–2959. [PubMed: 24239921]
15. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014; 311:806–814. [PubMed: 24570244]
16. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, Plomp K, van Bergen PF, Verheugt CL, Krivka E, de Vries CJ, Lok DJ, Grobbee DE, Mulder BJ. Social burden and lifestyle in adults with congenital heart disease. *Am J Cardiol*. 2012; 109:1657–1663. [PubMed: 22444325]
17. Ohuchi H, Miyamoto Y, Yamamoto M, Ishihara H, Takata H, Miyazaki A, Yamada O, Yagihara T. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. *American Heart Journal*. 2009; 158:30–39. [PubMed: 19540389]
18. Ohuchi H, Yasuda K, Ono S, Hayama Y, Negishi J, Noritake K, Mizuno M, Iwasa T, Miyazaki A, Yamada O. Low fasting plasma glucose level predicts morbidity and mortality in symptomatic adults with congenital heart disease. *International Journal of Cardiology*. 2014; 174:306–312. [PubMed: 24780541]
19. Martinez-Quintana E, Rodriguez-Gonzalez F, Nieto-Lago V, Novoa FJ, Lopez-Rios L, Riano-Ruiz M. Serum glucose and lipid levels in adult congenital heart disease patients. *Metabolism*. 2010; 59:1642–1648. [PubMed: 20423747]
20. Moon JR, Song J, Huh J, Kang IS, Park SW, Chang SA, Yang JH, Jun TG. Analysis of Cardiovascular Risk Factors in Adults with Congenital Heart Disease. *Korean Circ J*. 2015; 45:416–423. [PubMed: 26413110]
21. Deen JF, Krieger EV, Slee AE, Arslan A, Arterburn D, Stout KK, Portman MA. Metabolic Syndrome in Adults With Congenital Heart Disease. *J Am Heart Assoc*. 2016; 5:1–8.
22. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2009; 151:483–495. [PubMed: 19805771]
23. Eindhoven JA, van den Bosch AE, Oemrawsingh RM, Baggen VJ, Kardys I, Cuypers JA, Witsenburg M, van Schaik RH, Roos-Hesselink JW, Boersma E. Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease. *International Journal of Cardiology*. 2016; 202:246–251. [PubMed: 26402453]
24. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG, Rossouw JE, Wassertheil-Smoller S, Ridker PM. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women’s Health Initiative. *Circulation*. 2012; 125:1748–1756. S1741–1711. [PubMed: 22399535]
25. Roifman I, Therrien J, Ionescu-Ittu R, Pilote L, Guo L, Kotowycz MA, Martucci G, Marelli AJ. Coarctation of the aorta and coronary artery disease: fact or fiction? *Circulation*. 2012; 126:16–21. [PubMed: 22675158]

Figure 1a. Histograms depicting measures of lipid metabolism

Percentages are out of patients with lab values available (N). Distributions of lab values are shown in yellow, and regions of abnormal lab values are shown in red. The black segment at the base of the histogram spans the IQR, and a white dot marks the median.

Figure 1b. Histograms depicting measures of glucose and protein metabolism
 Percentages are out of patients with lab values available (N). Distributions of lab values are shown in yellow, and regions of abnormal lab values are shown in red. The black segment at the base of the histogram spans the IQR, and a white dot marks the median.

Figure 2a.

Distributions of ASCVD 10-year risk scores, Framingham risk scores, and Reynolds risk scores for patients in validated age range for each measure of 10-year CVD risk.

Figure 2b. Distributions of ASCVD 10-year risk scores, Framingham risk scores, and Reynolds risk scores for patients who have completed the fasting laboratory studies

CVD risk scores were calculated using the patient's actual age if it was within the age range where each tool was validated and using the boundary age closer to his/her actual age otherwise.

Table 1

Baseline Characteristics by Congenital Heart Disease Complexity.

Characteristic	All N=178	Lab Group N=103	Without Lab Group N=75	P-Value [*]
Age (mean±S.D.) (years)	37.1±12.6	38.4±12.8	35.4±12.1	0.120
Male	90 (51%)	52 (51%)	38 (51%)	> 0.999
Hispanic	25 (14%)	14 (14%)	11 (15%)	0.665
White	116 (65%)	68 (66%)	48 (64%)	0.905
Private insurance	133 (75%)	78 (76%)	55 (73%)	0.851
College education (Bachelors)	88 (49%)	55 (53%)	33 (44%)	0.277
Cardiac medication use	105 (59%)	65 (63%)	40 (53%)	0.248
NYHA functional classification				0.236
I: No limitation	78 (44%)	44 (43%)	34 (45%)	
II: Slight limitation	71 (40%)	43 (42%)	28 (37%)	
III: Marked limitation	18 (10%)	11 (11%)	7 (9%)	
IV: Severe limitation	5 (3%)	4 (4%)	1 (1%)	

* P-values were obtained via t-test for age and Pearson's chi-square test or Fisher's exact test for remaining categorical variables (race, insurance category, and education level were dichotomized as stated)

Table 2

Cardiovascular Risk Factors by Congenital Heart Disease Complexity

Risk Factor	All N=178	Lab Group N=103	Without Lab Group N=75	P-Value*
Gender male	90 (51%)	52 (51%)	38 (51%)	> 0.999
Age [†]	29 (16%)	17 (17%)	12 (16%)	> 0.999
Overweight/Obese	94 (53%)	54 (52%)	40 (53%)	> 0.999
Obese	38 (21%)	23 (22%)	15 (20%)	0.240
Systemic HTN	42 (24%)	29 (28%)	13 (17%)	0.134
Diabetes mellitus	8 (5%)	2 (2%)	6 (8%)	0.119
Dyslipidemia	35 (20%)	23 (22%)	12 (16%)	0.391
Smoker	4 (2%)	1 (1%)	3 (4%)	0.404
Physically inactive	23 (13%)	12 (12%)	11 (15%)	0.714
Family history of early CAD [‡]	19 (11%)	12 (12%)	7 (9%)	0.882

* P-values were obtained via Pearson's chi-square test or Fisher's exact test.

[†] 45 years of age for men and 55 years of age for women.

[‡] Death of first degree relative due to CAD before age 60.