Metabolic Syndrome in Adults With Congenital Heart Disease

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Background—Metabolic syndrome increases risk for atherosclerotic coronary artery disease, and its prevalence increases with increasing age and body mass index. Adults with congenital heart disease (ACHD) are now living longer and accruing coronary artery disease risk factors. However, the prevalence of metabolic syndrome in ACHD patients is unknown.

Methods and Results—We conducted a retrospective cohort study of ACHD patients at our center to quantify the prevalence of metabolic syndrome in an ACHD population. Using case-control matching, we constructed a comparable control group from a population-based sample of 150,104 adults. International Diabetes Federation criteria were used to define metabolic syndrome. We used logistic regression to compare the risk of metabolic syndrome across the resulting cohorts, which were composed of 448 ACHD patients and 448 controls matched by age and sex. Mean age of both groups was 32.4 ± 11.3 years, and 51.3% were female. Obesity was present in 16.1% of the ACHD patients and 16.7% of the controls. Metabolic syndrome was more common in ACHD patients than in controls (15.0% versus 7.4%; odds ratio 1.82, 95% CI 1.25–2.65).

Conclusions—Our data suggest that metabolic syndrome is more common among adults with congenital heart disease than in the general population. Thus, patients with congenital heart disease should be screened for metabolic syndrome and risk factors mitigated where possible to prevent atherosclerotic coronary artery disease. Preventive cardiology should be included during routine ACHD care. (J Am Heart Assoc. 2016;5:e001132 doi: 10.1161/JAHA.114.001132)

Key Words: atherosclerosis • congenital heart disease • metabolic syndrome • risk stratification
cohort with a matched, population-based control cohort of non-ACHD patients in Washington State.

Methods

Data Sources

We used the University of Washington ACHD registry to identify all patients ≥18 years old with a diagnosis of CHD who had clinic visits between 2009 and 2010. Demographic data available included age, sex, race, body mass index (BMI), and underlying cardiac diagnosis, as well as details on prior surgical repair. Patients were subcategorized as “simple” (simple complexity) or “complex” (moderate or great complexity) according to Bethesda Conference classification.

Available clinical data included serial systolic blood pressure and diastolic blood pressure, fasting lipid and blood glucose values, and medications for diabetes, hypertension, and dyslipidemia. The International Diabetes Foundation criteria were used to determine metabolic syndrome status. Patients with BMI ≥30 kg/m² without other criteria available to determine metabolic syndrome status were excluded from the final analysis. The production of a deidentified data set was approved by the Seattle Children’s Hospital Institutional Review Board.

The control group was derived from all adult patients seen through the Group Health Internal Medicine outpatient clinic in western Washington State between 2005 and 2006. Eligible patients were adults, aged 18 to 70 years, who lived in western Washington, had been continuously enrolled in the Group Health system for ≥6 months, and had an outpatient or specialty clinic visit with BMI recorded. Demographic and clinical data also available in the ACHD group were extracted from electronic medical records and automated databases, including clinical measures of height, weight, blood pressure, pharmacy fills, laboratory results, and International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes.

Patients without available height and weight data in the electronic medical record and patients with BMI ≥30 kg/m² without enough components available to determine metabolic syndrome status were excluded from the final analysis. The research use of these deidentified data was reviewed and approved by the Group Health Institutional Review Board.

For each patient in the ACHD and control group, metabolic syndrome status (presence or absence) was determined through data analysis software by using the International Diabetes Foundation criteria with BMI ≥30 kg/m² used as the central obesity criterion along with ≥2 of the following criteria: systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, diagnosis of hypertension or use of antihypertensive medications; fasting triglycerides ≥150 mg/dL or use of fibrates; high-density lipoprotein <40 mg/dL for men or <50 mg/dL for women or niacin use; and fasting blood glucose >100 mg/dL, diagnosis of diabetes, or use of antidiabetic medications (Table 1). Patients with BMI <30 or ≥30 kg/m² but negative for ≥3 other criteria were classified as not having metabolic syndrome. Central obesity was available for all subjects, but of the remaining criteria, only 2 positive or 3 negative results were required to determine metabolic syndrome.

Justification for Matching

Although the age criteria between control and ACHD were similar, we expected average age of the control group to be older. We anticipated this discrepancy because of the relatively lower life expectancy for patients with ACHD. Because of the data source, we also expected that many of the control patients would be less likely to have enough information to determine metabolic syndrome status. Missing components would generally occur for younger patients in the control group as annual laboratory tests are not recommended for healthy young adults. In contrast, subjects with diabetes and other known adverse health conditions are more likely to undergo frequent laboratory evaluations according to medical guidelines. Therefore, a relationship could exist between availability of laboratory data and metabolic syndrome. To reduce bias from these sources, we performed the case-control matching to construct groups of similar age and sex, in whom metabolic status could be determined for both members of the matched pair. The analysis including the entire control cohort may be biased because of age and data collection differences, both of which may be related to metabolic syndrome status.

Table 1. International Diabetes Foundation Worldwide Definition of Metabolic Syndrome

| Central Obesity (Defined as Waist Circumference* With Ethnicity-Specific Values) Plus Any 2 of the Following: |
|---------------------------------------------------------------|
| Hypertension                                                                                         |
| - Systolic blood pressure ≥130 mm Hg or                      |
|  - diastolic blood pressure ≥85 mm Hg or treatment of        |
|  - previously diagnosed hypertension                      |
| Hypertriglyceremia                                          |
| - ≥150 mg/dL or treatment for this lipid abnormality        |
| Reduced high-density lipoprotein                           |
| - <40 mg/dL in males or <50 mg/dL in females                |
|  - or treatment for this lipid abnormality                  |
| Fasting hyperglycemia                                      |
| - ≥100 mg/dL or previous diagnosed diabetes                |

*If body mass index is ≥30 kg/m², central obesity can be assumed and waist circumference does not need to be measured.
Statistical Analysis

Before matching, the ACHD group and the control group were treated as independent samples. Baseline characteristics and components of metabolic syndrome were compared across these groups with use of the t-test for independent samples for continuous variables and Pearson’s χ² test for categorical variables.

ACHD patients were matched to a control patient in a 1:1 ratio by using a greedy matching algorithm, matching sex exactly and age within 1 year. If multiple matches were available, one was selected at random to remove any potential bias. Metabolic syndrome status was then determined. If metabolic syndrome status could be determined for both members of the matched pair, then the pair was included. To account for possible discrepancies in missing data between study and control populations, the pair was excluded if metabolic syndrome status could not be determined for one or both members of the matched pair. Individual components of metabolic syndrome were not statistically compared across matched cohorts because the matched groups are not independent. However, we did not require the individual components of metabolic syndrome to be available for inclusion in the primary incidence comparison as long as metabolic syndrome status could be determined for both members of the matched pair. Descriptive statistics were provided for each group, and percentages are based on the number with data for each component. Odds ratios (Ors) for the risk of metabolic syndrome were calculated by using conditional logistic regression, adjusted for the matching variables.

The primary outcome was risk of metabolic syndrome for ACHD patients relative to the matched controls. There were no adjustments for multiple comparisons, and all P-values and CIs shown in the results are 2-sided.

Data were analyzed by using SAS® version 9.4 (SAS Institute), and graphs were produced by using R (R Foundation for Statistical Computing).

Results

The ACHD cohort (aged 18–70) consisted of 599 patients, and metabolic syndrome status could be determined in 91%; therefore, 543 ACHD patients were included in the final analysis. Specific types of cardiac lesions for the total ACHD cohort are presented in Table 2. Of the 150 104 patients in the population-based sample from which the control group was derived, metabolic syndrome status could be determined in 90% (Figure 1). In 134 925 patients in whom metabolic syndrome status could not be determined, the population-based patients were significantly older (mean age 48.1 versus 32.3, P<0.001), more likely to be female (63.9% versus 52.1%, P<0.001), more likely to be obese (28.7% versus 16.6%, P<0.001), and had a greater mean BMI (28.2 versus 25.6 kg/m², P<0.001) (Table 3). After adjustment for age and sex, the OR for metabolic syndrome in ACHD patients compared with all control patients was 1.75 (95% CI 1.38–2.22, P<0.001) (Figure 2).

After 1:1 case-control matching, 448 ACHD and 448 control patients were included in the matched cohort analysis (Table 4). Obesity rate was similar between the matched ACHD and control groups, although mean BMI for the ACHD group was slightly lower (25.5±6.3 kg/m² versus 26.9±8.3 kg/m² in the control group). Further, age was similar between the groups among subjects who met each of the metabolic syndrome criteria. On examination of individual metabolic syndrome risk factors, ACHD patients were more likely to have elevated triglyceride levels (36.9% versus 15.9%), low high-density lipoprotein levels (59.5% versus 14.4%), and elevated fasting plasma glucose levels (40.4% versus 9.2%), while controls were more likely to be hypertensive (46.0% versus 35.9%). In addition, obese patients with

### Table 2. Types of Cardiac Malformations Seen in Total Adults With Congenital Heart Disease Cohort and Proportion With Metabolic Syndrome

| Cardiac Malformation (N=543) | No. (%) | Metabolic Syndrome, n (%) | Median Age, y |
|-----------------------------|---------|---------------------------|---------------|
| Tetralogy of Fallot          | 95 (17) | 15 (16)                   | 30 (19–74)    |
| Valvular disease             | 86 (16) | 16 (19)                   | 29 (19–77)    |
| Aortic arch anomalies        | 77 (14) | 9 (12)                    | 28 (19–67)    |
| d-Transposition of the great arteries | 51 (9) | 5 (10)                   | 27 (18–51)    |
| Fontan procedure             | 43 (8)  | 6 (14)                    | 27 (19–48)    |
| Ventricular septal defect    | 21 (4)  | 4 (19)                    | 28 (21–46)    |
| Atrioventricular septal defect | 21 (4) | 6 (29)                    | 24 (21–36)    |
| Congenitally corrected transposition of the great arteries | 20 (4) | 6 (30) | 36.5 (20–63) |
| Anomalous pulmonary venous return | 20 (4) | 3 (15) | 42 (20–79) |
| Ebstein anomaly              | 16 (3)  | 4 (25)                    | 35.5 (23–70)  |
| Atrial septal defect         | 11 (2)  | 3 (27)                    | 27 (18–54)    |
| Coronary artery anomaly      | 8 (1)   | 0 (0)                     | 26.5 (18–61)  |
| Eisenmenger physiology       | 8 (1)   | 0 (0)                     | 34.5 (25–43)  |
| Pulmonary atresia with intact ventricular septum | 8 (1) | 1 (13) | 25 (19–33) |
| Truncus arteriosus           | 7 (1)   | 1 (14)                    | 29 (23–39)    |
| Other                        | 51 (9)  | 4 (2)                     | NA            |

NA indicate not applicable.
CHD were more likely to have metabolic syndrome than were obese controls (93.1% versus 44.0%) (Table 4).

Within the matched cohorts, 15.0% ACHD patients met International Diabetes Foundation criteria for metabolic syndrome versus 7.4% of control patients. After controlling for the matching variables, the OR comparing ACHD patients with control patients for metabolic syndrome was 1.82 (95% CI 1.25–2.65, \( P = 0.002 \)) (Figure 2).

In the ACHD group, 103 patients with simple CHD and 440 patients with complex CHD were identified (Table 5). Age and BMI were similar across disease complexity. Although none of these comparisons reached significance in these small subgroups, patients in the simple group were more likely to have an elevation in triglyceride levels (45.2% versus 35.9%), and \( \approx 5\% \) more likely to be female, while the complex group had lower high-density lipoprotein levels (62.9% versus 50.0%). Presence of hypertension did not differ between groups. The prevalence of metabolic syndrome was 13.6% for simple CHD and 15.7% for complex CHD (\( P=0.596 \)). In comparing ACHD patients within each subgroup with their matched controls, the ORs for metabolic syndrome were 2.16 for simple (95% CI 0.83–5.59, \( P=0.113 \)) and 1.76 for complex CHD (95% CI 1.17–2.65, \( P=0.007 \)) (Figure 2).

**Discussion**

Defining risk for metabolic syndrome in an ACHD population poses several challenges. The adult cohort is growing as the

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**Table 3. Comparison of Adults With Congenital Heart Disease (ACHD) and Unmatched Control Group Where Metabolic Syndrome Could be Determined**

|                      | ACHD Patients (n=543) | Control Patients (n=134 925) | \( P \) Value |
|----------------------|-----------------------|-----------------------------|--------------|
|                      | No. of Patients | Mean±SD, or n | No. of Patients | Mean±SD, or n |              |
| Age                  | 543               | 32.3±11.0 y | 134 925         | 48.1±13.6 y | <0.001      |
| Female sex           | 543               | 283 (52.1%) | 134 925         | 86 221 (63.9%) | <0.001      |
| Body mass index      | 543               | 25.6±6.34 kg/m² | 134 925 | 28.2±6.80 kg/m² | <0.001      |
| Central obesity (body mass index \( \geq 30 \) kg/m²) | 543 | 90 (16.6%) | 134 925 | 38 738 (28.7%) | <0.001      |
| Hypertension         | 543               | 191 (35.2%) | 134 925         | 88 819 (65.8%) | <0.001      |
| Hypertriglyceridemia | 184               | 69 (37.5%) | 91 168          | 26 183 (28.7%) | 0.009       |
| Reduced high-density lipoprotein | 187 | 113 (60.4%) | 91 168 | 14 660 (16.1%) | <0.001      |
| Fasting hyperglycemia | 183            | 71 (38.8%) | 134 925         | 22 305 (16.5%) | <0.001      |
| Metabolic syndrome criteria met | 543 | 83 (15.3%) | 134 925 | 22 390 (16.6%) | 0.413       |
pediatric CHD population ages. Further, these patients are frequently lost to follow-up, diminishing the subject numbers for data collection. We performed our study within the confines of a well-established ACHD program within a tertiary center that transitions patients from a large academic pediatric cardiology center. Admittedly, this study therefore presents a somewhat biased ACHD population with robust follow-up and evaluation. However, our strategy provides for a relatively large subject number with complete data sets for assessment of metabolic syndrome and cardiovascular risk. Within this context, our ACHD population represents the largest cohort reported to date in regard to the prevalence of the metabolic syndrome.

Issues related to selection of an appropriate control group have also limited the value of findings from some prior studies, which attempted to evaluate obesity rates in ACHD. For instance, national data have been used to compare with local ACHD populations, thereby ignoring the impact of regional variations. In our study, we used a large regional cohort consisting of control subjects who were evaluated regularly as standard practice within a health maintenance organization. Thus, our study provides comparisons with actual hard clinical data sets, as opposed to using subject survey-based data such as is used in the National Health and Nutrition Examination Survey.

We used 2 independent strategies to compare obesity and metabolic syndrome prevalence between our ACHD and control populations. First, we used the extended power provided by the large subject numbers within the control population. Although the analyses showed highly significant differences in prevalence for metabolic syndrome, we believed that study result interpretation could be impaired as a result of age and sex discrepancies existing between the study populations. Therefore, we followed with age and sex greedy matching strategy, which obviated the impact of these discrepancies. This latter commonly used method for large cohort studies identified a >2-fold risk for metabolic syndrome in the ACHD group compared with controls.

Although our unmatched data and results from previous smaller studies suggest that obesity prevalence is lower in certain ACHD populations, several recent studies have found...
that individuals with complex CHD have an increased prevalence of obesity after the Fontan operation.\textsuperscript{16-18} We found similar obesity rates between ACHD and control groups by using our greedy matching algorithm. This discrepancy highlights the importance of accounting for age and sex when defining these risk factors in the ACHD population. Accordingly, we further identified elevated risk of metabolic derangements in ACHD patients, consistent with decreased insulin sensitivity. These study results conform to previously published findings of abnormal glucose tolerance and low high-density lipoprotein levels in ACHD patients.\textsuperscript{19,20} Ohuchi et al reported lower fasting but higher postprandial blood glucose and glycated hemoglobin levels in adult Japanese who had no repair or Fontan patients compared with healthy controls.\textsuperscript{20} However, their study again illustrates some confounding design factors, including lack of age and sex matching, as well as a fairly small control group.

We divided the study ACHD cohort into simple and complex CHD based on the Bethesda Conference classification system.\textsuperscript{15} The conference recommended that patients with simple CHD be cared for in the general medical community but that patients with moderate- and great-complexity CHD (which comprise our complex subgroup) require lifelong care in a regional ACHD center. Subgroup analyses for the matched cohorts showed the prevalence of metabolic syndrome differed between complex CHD and the matched controls. However, the incidence in the simple group was not significantly different compared with the controls. Lack of significance for the simple subgroup may be due to inadequate power for the smaller simple cohort or may truly reflect a similar risk of developing acquired cardiovascular risk factors as the general population. Overall and in subgroups of surgical complexity, the point estimates of the ORs were >1, suggesting that CHD and metabolic syndrome may be linked regardless of cardiac lesion complexity.

Similar to the general population, obesity creates the major risk for development of metabolic syndrome in ACHD patients. Little is known about the long-term effects of obesity on patients with CHD. Our results raise the question of whether increased propensity to obesity-related cardiovascular risk factors exists in obese CHD patients. The obesity prevalence in children and adults with CHD approximates that observed in the general population. However, CHD patients possess unique risk factors for developing obesity, including exercise restriction and differing nutritional strategies in infancy.\textsuperscript{11-14}

Exercise restriction is common in patients with CHD and has been shown to promote obesity in children with CHD.\textsuperscript{14} Some restrictions on competitive sports are recommended in certain high-risk populations. Most patients with repaired CHD may exercise safely, but medical providers, as well as parents and caregivers, often impose additional unwanted exercise restrictions.\textsuperscript{21,22} Further, ACHD patients frequently self-restrict exercise because of perceived risks of underlying CHD or because of limited capacity for exercise.\textsuperscript{23,24} Aside from predisposing to obesity and hyperlipidemia, the lack of aerobic exercise is associated with an increased risk of hospitalization and death in ACHD patients.\textsuperscript{14,23,25} Enhanced physical activity and aerobic exercise play an important role in decreasing cardiovascular risk.\textsuperscript{25} However, questions remain regarding this effect in CHD patients.

Patients with severe forms of CHD often exhibit failure to thrive early in life and require increased caloric supplementation via alternative feeding protocols to achieve appropriate weight gain in infancy, but they experience a period of rapid growth toward peer norms once palliation via cardiac surgery is performed.\textsuperscript{26} Similar growth patterns seen in infants without CHD are associated with obesity and a greater risk of adult cardiovascular disease.\textsuperscript{27,28} In addition, although

### Table 5. Comparison of Adults With Congenital Heart Disease (CHD) Group by Bethesda Conference Classification Subgroup

|                        | Simple CHD (n=103) | Complex CHD (n=440) | P Value |
|------------------------|--------------------|---------------------|---------|
| No. of Patients | Mean±SD, or n   | No. of Patients | Mean±SD, or n   |
| Age                  | 103                | 32.6±11.9 y        | 440      | 32.2±10.9 y        | 0.764 |
| Female sex           | 103                | 58 (56.3%)         | 440      | 225 (51.1%)        | 0.344 |
| Body mass index      | 103                | 25.3±7.02 kg/m²    | 440      | 25.7±6.18 kg/m²    | 0.557 |
| Central obesity (body mass index ≥30 kg/m²) | 103                | 14 (13.6%)         | 440      | 76 (17.3%)         | 0.366 |
| Hypertension         | 103                | 37 (35.9%)         | 440      | 154 (35.0%)        | 0.86  |
| Hypertriglyceridemia  | 31                 | 14 (45.2%)         | 153      | 55 (35.9%)         | 0.334 |
| Reduced high-density lipoprotein | 32               | 16 (50.0%)        | 155      | 97 (62.6%)         | 0.185 |
| Fasting hyperglycemia | 30                | 14 (46.7%)         | 153      | 57 (37.3%)         | 0.333 |
| Metabolic syndrome criteria met | 103                | 14 (13.6%)         | 440      | 69 (15.7%)         | 0.596 |
most children have normal nutritional requirements after surgical palliation, medical providers and parents may continue to stress weight gain as a goal. Further studies are warranted to examine the relation of feeding protocols and growth patterns seen in infants with complex CHD and acquired cardiovascular risk factors. The observed prevalence of obesity and metabolic syndrome was markedly lower in our control population compared with the US population as a whole, where metabolic syndrome prevalence is estimated at 34% to 39% and ≈35.5% of US adults are obese. The difference may reflect a failure of providers to screen all adult patients for each the components of the metabolic syndrome in routine clinical practice. Prior population-based estimates of the prevalence of metabolic syndrome relied on heavily screened populations. It may also represent underlying socioeconomic, racial, or geographic differences. Group Health enrollees are demographically similar to the area population in western Washington, but compared with the national US population, the cohort has fewer racial/ethnic minorities. This regional variation is seen in the ACHD population as well, in regard to obesity prevalence, with patients in western Washington State exhibiting lower obesity prevalence than patients in other regions of the country.

Limitations
The limitations to our study are primarily related to the factors, inherent in the retrospective cohort design. Data for the study and control group were available only for a fixed period of time (2009–2010 and 2005–2006, respectively), and glucose and cholesterol measures were available for patients in whom these tests were indicated during this window. If the recommended screening interval did not occur in the sample window, data may not have been collected for healthy adults. We believe the absence of this clinical data is random, as there are well-established guidelines in regard to universal screening of cardiovascular disease risk factors in adults. Also, the different data collection times for the study and control groups may have introduced an untoward cohort effect, while noting that obesity prevalence in Washington State increased between 2005 and 2009. Potentially important variables, including race/ethnicity, socioeconomic status, smoking and other comorbidities, were not available in the control data, so this information could not be used to improve the matching or to otherwise assess whether difference in incidence may be related to differences in these variables. Last, our study relies solely on regional data; therefore, our findings may not be representative of the US population as a whole and may not represent specific ethnic populations.

Conclusions
Our study demonstrates an increased prevalence of metabolic syndrome in ACHD patients in western Washington State, and this result may reflect an increased risk for ACHD patients nationwide. Preventive cardiology, including healthy lifestyle counseling, blood pressure monitoring, and close screening for lipid abnormalities and insulin resistance, should be performed for ACHD patients. Exercise capacity should be evaluated and appropriate aerobic activities should be encouraged in most ACHD patients. Additionally, because atherosclerosis as a disease entity is known to have its origins in the pediatric age group, pediatric cardiologists have a role in preventative cardiology counseling in children with CHD and should follow the current screening guidelines for cardiovascular health.

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Disclosures
None.

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