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## Substantial Cardiovascular Morbidity in Adults with Lower-Complexity Congenital Heart Disease

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### Abstract

**Background:** Although lower-complexity cardiac malformations constitute the majority of adult congenital heart disease (ACHD), the long-term risks of adverse cardiovascular events and relationship with conventional risk factors in this population are poorly understood. We aimed to quantify the risk of adverse cardiovascular events associated with lower-complexity ACHD that is unmeasured by conventional risk factors.

**Methods:** A multi-tiered classification algorithm was used to select individuals with lower-complexity ACHD and individuals without ACHD for comparison amongst >500,000 British adults in the UK Biobank (UKB). ACHD diagnoses were sub-classified as “isolated aortic valve (AoV)” and “non-complex” defects. Time-to-event analyses were conducted for primary endpoints of fatal or non-fatal acute coronary syndrome (ACS), ischemic stroke, heart failure (HF), and atrial fibrillation, and a secondary combined endpoint for major adverse cardiovascular event (MACE).

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None.

Maximum follow-up time for the study period was 22 years using retrospectively and prospectively collected data from the UKB.

**Results:** We identified 2,006 individuals with lower-complexity ACHD and 497,983 unexposed individuals in the UKB (median [IQR] age at enrollment 58 [51,63]). Of the ACHD-exposed group, 59% were male; 51% were current or former smokers; 30% were obese; 69%, 41%, and 7% were diagnosed or treated for hypertension, hyperlipidemia, and diabetes respectively. After adjustment for 12 measured cardiovascular risk factors, ACHD remained strongly associated with the primary endpoints, with hazard ratios (HR) ranging from 2.0 (95% confidence interval [CI] 1.5–2.8,  $p < 0.001$ ) for ACS to 13.0 (95% CI 9.4–18.1,  $p < 0.001$ ) for HF. ACHD-exposed individuals with 2 cardiovascular risk factors had a 29% age-adjusted incidence rate of MACE in contrast to 13% in non-ACHD individuals with 5 risk factors.

**Conclusions:** Individuals with lower-complexity ACHD had higher burden of adverse cardiovascular events relative to the general population that was unaccounted for by conventional cardiovascular risk factors. These findings highlight the need for closer surveillance of patients with mild to moderate ACHD and further investigation into management and mechanisms of cardiovascular risk unique to this growing population of high-risk adults.

### Keywords

adult congenital heart disease; adverse events complication; acute coronary syndrome; atrial fibrillation; heart failure; ischemic stroke

## Introduction

For children born with congenital heart disease, surviving to adulthood is now the norm. With the adult congenital heart disease (ACHD) population exceeding the population of affected children<sup>1</sup>, the burden of morbidity and mortality has shifted towards acquired diseases of adulthood. Population-based and institutional ACHD registries demonstrate a high prevalence of coronary artery disease (CAD)<sup>2–4</sup>, stroke<sup>5,6</sup>, heart failure<sup>7,8</sup>, arrhythmia<sup>9,10</sup>, and associated other cardiometabolic conditions<sup>11–13</sup> in the ACHD population, specifically among those with more complex lesions.

While adults with lesions of high complexity (e.g., single ventricles) increasingly receive comprehensive cardiovascular care in ACHD clinics, those with simpler lesions (e.g., isolated septal or valvular defects) have measurably less consistent participation in specialized clinics and research studies<sup>14,15</sup>, and thus the risk of cardiac complications in the latter population is not well understood. Furthermore, the contribution of traditional risk factors to acquired cardiovascular disease has been difficult to characterize owing to limitations in population-scale ascertainment of risk factors in regionally fragmented systems of care for this population.

Here, we assess the relationship between lower complexity ACHD and cardiovascular disease risk using the UK Biobank, a large prospective population-based cohort of over 500,000 individuals with long-term follow-up. Specifically, we characterize the burden of cardiovascular risk factors and disease incidence in a real-world ACHD population primarily comprised of lower-complexity cardiac malformations and quantify the risk for adverse

cardiovascular events associated with ACHD that is unaccounted for by traditional cardiovascular risk factors.

## Methods

The data for this study is publicly available to registered investigators of the UK Biobank, and the analytic methods are made available online by the authors at [https://github.com/priestlab/Circulation\\_2019\\_Saha](https://github.com/priestlab/Circulation_2019_Saha).

### Study population

The study cohort was derived from the UK Biobank (UKB), a large prospective cohort study with comprehensive health data from over 500,000 volunteer participants in the United Kingdom aged 37–73 years at recruitment in 2006–2010. The cohort has previously been described in detail<sup>16,17</sup>. Studies using the UKB are exempt from Institutional Review Board approval as the data is de-identified and publicly available.

### Classification of Adults with Congenital Heart Disease

Congenital heart disease was defined as any structural cardiac abnormality, inclusive of bicuspid aortic valve, present in the heart or adjoining great vessels from birth in the absence of syndromic illness (i.e., syndromes characterized by extra-cardiac or neurocognitive manifestations in addition to cardiac malformations). A multi-step classification algorithm (Figure 1, Supplemental Tables 1–4, Supplemental Methods) was developed to ascertain 2,102 individuals with non-syndromic ACHD and 497,983 non-ACHD comparison individuals using hospital encounter statistics (HES) and self-reported medical history in the UKB.

Individuals with ACHD were further organized into mutually exclusive subgroups based on lesion (Figure 1, Supplemental Table 5). The “isolated aortic valve (AoV) defects” subgroup (n = 1,082), which represents the largest uniform subtype of ACHD in the UKB, is comprised of individuals with congenital aortic insufficiency and/or stenosis (ICD9: 746.3, 746.4, ICD10: Q23.0, Q23.1) or inferred through ancillary diagnostic evidence to have an AoV defect (Supplemental Methods, Supplemental Figure 1). “Complex” defects (n = 96), adapted in part from the definition of “severe” congenital heart disease by Marelli and colleagues<sup>18</sup>, represents lesions with high likelihood of cyanosis and is comprised of single ventricles, transposition complex, truncus arteriosus, tetralogy of Fallot, atrioventricular canal defect, and total anomalous pulmonary venous return. All remaining lesions, the majority being left-to-right shunt defects, were categorized as “non-complex” defects (n = 924). Only the isolated AoV defects and non-complex defects subgroups – representing mild to moderate ACHD – were considered for analysis in this study.

### Outcome phenotype definitions

Cardiovascular outcomes were defined using ICD-9, ICD-10, and OPCS-4 codes from the HES and death registries as well as self-reported non-cancer illnesses and operations; definitions were adapted in part from previously described methods (Supplemental Methods). The primary endpoints for survival analysis were first occurrence of fatal or non-

fatal acute coronary syndrome (ACS), ischemic stroke, heart failure (HF), and atrial fibrillation (AF) respectively. In secondary and sensitivity analyses, a combined endpoint of major adverse cardiovascular event (MACE), defined as first occurrence of any of the primary endpoints, was used. Owing to the availability of hospital admissions data predating the enrollment period, the follow-up period for each individual in this study spanned from 10 years prior to enrollment in the UKB until occurrence of a primary endpoint, death, or censorship from UKB. This allowed for a maximum of 22 years of follow-up.

Continuous covariates used in fully adjusted multivariable Cox regression analyses were age, Townsend deprivation index (a validated measure of socioeconomic status in the United Kingdom)<sup>19</sup>, body mass index, systolic blood pressure and diastolic blood pressure. Categorical covariates used in Cox regression were sex, ethnicity (Caucasian, non-Caucasian), smoking status (current, former, never), alcohol consumption (daily, weekly, seldom), physical activity (low versus high, where “low” is defined as not satisfying WHO recommendation of at least three days per week of vigorous intensity activity or five days per week of moderate intensity exercise), family history of cardiovascular disease, history of hypertension and/or use of anti-hypertensive medications, history of hyperlipidemia diagnosis and/or use of statins, and history of diabetes diagnosis and/or use of insulin (Supplemental Methods, Supplemental Table 6). Covariates were measured at the time of enrollment and considered to be stable proxy measures for the span of the follow-up period (Supplemental Methods, Supplemental Table 7).

### Statistical Analysis

Statistical analyses were performed using the ‘survival’ and ‘survminer’ statistical packages in R version 3.4.3. Sociodemographic, lifestyle, and cardiometabolic covariates were compared across groups using Chi-squared tests for categorical variables and Wilcoxon rank sum test for continuous variables (assuming non-normal distributions).

Cumulative incidence curves were generated for each of the primary endpoints. A multi-state model<sup>20</sup> was utilized to take into account the competing risk of death and potential mediation effects between the primary endpoints. Multivariable Cox proportional hazards regression was then used to estimate hazard ratios (HR) and 95% confidence intervals (CI) after adjusting for continuous and categorical covariates mentioned previously. Adherence of survival analyses to the underlying proportional hazards assumption was assessed using the Schoenfeld residuals test.

Individuals were then stratified into three categories of cardiovascular risk based on the number present out of eight classical CV risk factors (male sex, current/former smoking status, obesity [i.e. BMI >30], low physical activity, family history of cardiovascular disease, diagnosis/treatment for hypertension, diagnosis/treatment for hypercholesterolemia, diagnosis/treatment for diabetes). Low ( 2), intermediate (=3–4), and high ( 5) number of cardiovascular risk factors were equivalent to risk tertiles. Direct standardization was employed to estimate age-adjusted incidence rates for MACE at each level of cardiovascular risk over the 22-year follow up period. Cox proportional hazards regression was used to estimate HRs for MACE associated with ACHD at each stratum of cardiovascular risk, adjusted for age, ethnicity, and Townsend deprivation index.

## Sensitivity Analyses

Given the known risk of acquiring cardiac morbidity acutely in the perioperative setting, a sensitivity analysis was performed on the multi-state Cox regression models for each primary endpoint in which individuals who had undergone cardiac surgery within one year prior to the event of interest were excluded from analysis (Supplemental Table 8).

Sensitivity analyses were undertaken to assess for potential misclassification of ACHD cases resulting from inference of ACHD using non-specific diagnostic codes (Supplemental Tables 9–12). In sensitivity analysis A (Supplemental Table 9), HRs for the isolated AoV defects group were estimated with both inclusion and exclusion of diagnostic codes specific for congenital aortic insufficiency and/or stenosis to assess for the effect of inferred cases on the estimates. In sensitivity analysis B (Supplemental Table 10), the isolated AoV defects group was restricted to include inferred cases who were ascertained to have a valve defect using an earlier diagnostic age cutoff (aortic stenosis/insufficiency diagnosed at <50 years and/or aortic valve replacement at <55 years), thereby increasing the likelihood that the cause of valvular disease was due to a congenital malformation and not acquired calcific valvular disease (Supplemental Figure 1). In sensitivity analysis C (Supplemental Table 11), individuals who had undergone aortic valve replacement procedures were excluded from the cohort to assess for selection bias since aortic valve replacement was a qualifying inclusion criterion for inference of isolated AoV defects. In sensitivity analysis D (Supplemental Table 12), individuals who had an unspecified non-complex defect (i.e. heart surgery prior to age 18 and/or non-specific diagnostic code for congenital heart disease) were excluded from analysis to assess for misclassification bias in the non-complex defects subgroup.

## Results

### Clinical Characteristics of Study Population

We identified 2,006 participants with mild to moderate ACHD, comprising 1,082 participants with isolated AoV defects and 924 with non-complex defects, and 497,983 individuals for comparison from the UKB. Cardiac MRI data from 8 standard anatomical sequences were available for >20,000 individuals in the UKB; of 32 ACHD cases with available imaging data, 29 displayed clear confirmatory visual evidence of the assigned ACHD diagnosis yielding a specificity of 91% for our ACHD classification algorithm (Supplemental Figure 2).

The socio-demographic, lifestyle, and cardiometabolic characteristics shown in Table 1 demonstrate a higher burden of CV risk factors among the ACHD cohort, including male predominance (59% versus 46%,  $p<0.001$ ), slightly higher material deprivation (median Townsend Deprivation Index  $-1.74$  versus  $-2.14$ ,  $p<0.001$ ), and a higher proportion of current or former smokers (51% versus 46%,  $p<0.001$ ). Several cardiometabolic risk factors were more prevalent in the exposed versus the unexposed individuals, such as obesity (30% versus 24%,  $p<0.001$ ), hypertension (69% versus 55%,  $p<0.001$ ), hyperlipidemia (41% versus 19%,  $p<0.001$ ), and diabetes (6.7% versus 3.8%,  $p<0.001$ ). Both the isolated AoV and non-complex defects subgroups followed the composite ACHD trends, with the exception of a similar proportion of men (46%) and a lower rate of current or former

smoking (44%) in the non-complex defects group relative to the comparison group. The isolated AoV defects group generally displayed a higher frequency of risk factors than the non-complex defects group. There were no significant differences between the ACHD subgroups and the comparison group in age at enrollment, ethnicity, alcohol consumption, physical activity, and family history of cardiovascular disease.

### Unadjusted Cumulative Incidence of Cardiovascular Morbidity

Over a median of 20 years of follow-up centered on the time of enrollment into the UKB, the unadjusted incidence of all primary endpoints occurred at a higher rate for ACHD-exposed individuals than non-ACHD comparison individuals (Figure 2). By the end of the follow-up period, 5–12% of the ACHD cohort had suffered incident ACS, ischemic stroke, and/or HF and 20% had suffered from AF, compared to less than 5% incidence of all endpoints for the non-ACHD population in this cohort. After adjusting for only sociodemographic factors (age, sex, ethnicity, and Townsend deprivation), the non-complex ACHD subgroup demonstrated a significantly higher hazard of AF ( $p = 0.00003$ ) and ischemic stroke ( $p=0.007$ ) than the isolated AoV defects subgroup. There was no significant difference in incidence rates of ACS and HF between the two ACHD subgroups.

### Multivariable-Adjusted Multi-State Cox Regression Analysis

After adjustment for common cardiovascular risk factors (i.e., age, sex, ethnicity, Townsend Deprivation index, smoking status, alcohol consumption, physical activity, family history of cardiovascular disease, BMI, hypertension, hyperlipidemia, diabetes), ACHD exposure continued to be strongly associated with the primary endpoints (Table 2). Sensitivity analyses did not suggest that incident events were temporally related to perioperative risk (Supplemental Table 8) or bias in classification (Supplemental Tables 9–12). The outcome with highest risk was HF, demonstrating no significant difference ( $p=0.75$ ) between individuals with isolated AoV defects (adjusted HR [aHR] 12.2 [95% CI 9.5–15.6],  $p<10^{-16}$ ) and with non-complex defects (aHR 13.0 [95% CI 9.4–18.1],  $p<10^{-16}$ ). Ischemic stroke and AF continued to demonstrate higher hazard in the non-complex defects subgroup (ischemic stroke: aHR 5.1 [95% CI 3.9–6.6],  $p<10^{-16}$ ; AF: aHR 13.0 [95% CI 11.1–15.2],  $p<10^{-16}$ ) than in the isolated AoV defects subgroup (ischemic stroke: aHR 2.2 [95% CI 1.7–2.9],  $p=1.3 \times 10^{-8}$ ; AF: aHR 7.5 [95% CI 6.4–8.7],  $p<10^{-16}$ ),  $p$ -value for comparison significant only for AF. Strikingly, the risk of ACS displayed similar aHR in both ACHD subgroups (isolated AoV: aHR 2.1 [95% CI 1.7–2.5],  $p=1.5 \times 10^{-11}$ ; non-complex: aHR 2.0 [95% CI 1.5–2.8],  $p=8.7 \times 10^{-6}$ ),  $p=0.95$  for comparison.

### Stratification by Level of Cardiovascular Risk

To compare the risk of MACE in individuals with and without ACHD across different levels of cardiovascular risk, we stratified all participants by the number of cardiovascular risk factors present into low (0–2), intermediate (3–4), or high (5–8) risk tertiles. When stratified by cardiovascular risk level, the ACHD population continued to show dramatically greater age-adjusted absolute incidence of MACE when compared to the comparison group in the same cardiovascular risk stratum (Figure 3A). Compared across risk strata, the absolute incidence of MACE for the ACHD subgroups in the lowest stratum of cardiovascular risk (30.5% [95% CI 22.1–39.6%] for isolated AoV and 27.5% [95% CI 21.2–34.2%] for non-

complex) was more than double that of the comparison group at the highest level of cardiovascular risk (13.1% [95% CI 12.8–13.3%]). The risk of MACE relative to the non-ACHD comparison group was most pronounced among the two ACHD subgroups with 2 cardiovascular risk factors (aHR 15.9 [95% CI 11.9–21.2] for isolated AoV defects and aHR 15.3 [95% CI 12.1–19.4] for non-complex defects), whereas the relative risk was lower in the setting of 5 cardiovascular risk factors (aHR 4.3 [95% CI 3.7–4.9] for isolated AoV defects and aHR 4.4 [95% CI 3.6–5.4] for non-complex defects) (Figure 3B). Age-adjusted incidence by risk strata for individual primary endpoints are shown in Supplemental Figure 3.

The disparate risk estimates for MACE at different strata of cardiovascular risk suggested interaction between the cardiovascular risk factors and ACHD. Tests for interaction between the ACHD subgroups and individual CV risk factors (Supplemental Table 13) demonstrated that the presence of ACHD significantly modified the effects of sex, hypertension, and hyperlipidemia on the risk of MACE (significant at  $p < 0.003$  after Bonferroni correction). Furthermore, the estimated beta coefficients for the interaction terms between ACHD and the aforementioned risk factors were all less than zero, demonstrating that the effect of the risk factors was relatively smaller in the ACHD-exposed group than the unexposed comparison group. These results imply that traditional cardiovascular risk factors may have a less pronounced, albeit still significant, role in conferring risk for MACE in the ACHD versus non-ACHD population.

## Discussion

In this population-based study of ACHD-associated risk of cardiovascular disease, we observed a substantial burden of adverse cardiovascular events in a cohort of older adults with simple to moderately complex ACHD. We discerned substantial residual risk for adverse cardiovascular events in the ACHD cohort that is disproportionate to the burden of known cardiovascular risk factors noted in this subgroup of the UKB. These findings provide further evidence for a cardiovascular disease risk profile unique to individuals with mild to moderate ACHD and highlight the need to extend preventive care practices beyond the management of conventional risk factors for this population.

The residual risk of adverse cardiovascular events after adjusting for conventional risk factors was considerably higher in individuals with ACHD compared to the general UKB population, ranging from a 2-fold increased risk of ACS to a 13-fold increased risk of HF. Our estimates are similar in magnitude to risk estimates derived from younger ACHD populations that were adjusted for only a small number of conventional cardiovascular risk factors<sup>21–24</sup>. At a median enrollment age of 58, the ACHD cohort – particularly individuals with isolated AoV defects – in the UKB had a higher frequency of current or former smokers, obesity, hypertension, hyperlipidemia, and diabetes than the rest of the UKB. Other ACHD cohorts comprising younger individuals (median age of 28–29) were observed to have higher rates of obesity, hypertension, and diabetes, indicating that such risk factors may be present from early adulthood<sup>5,22,25</sup>.

Despite an overall higher burden of cardiovascular risk factors in the ACHD cohort, we observed a significantly higher incidence of MACE in the ACHD subgroups than the general UKB population when comparing individuals at similar levels of cardiovascular risk. Among those with two or fewer cardiovascular risk factors, there was a 29% age-adjusted incidence of MACE in the ACHD cohort compared to only 3% incidence among the comparison group, suggesting that ACHD-associated risk mechanisms are key determinants of cardiovascular risk in the ACHD population irrespective of conventional risk factors. As has been hypothesized<sup>25,26,24</sup>, ACHD-associated factors may even modify the effect of conventional risk factors as suggested by the variation in relative risk at different risk levels. Notably, as the ACHD population in this study represents mild to moderate lesions – valvular and septal defects being the most common subtypes, these findings further emphasize the critical importance of surveillance of this highly prevalent ACHD subgroup which often lacks long-term clinical follow-up<sup>26,27</sup> despite having higher risk of mortality and morbidity compared to the general population<sup>10,28,29</sup>.

While the long-term risks of HF and arrhythmia associated with ACHD are well described<sup>8,30,31</sup>, morbidity from ACS and stroke in the ACHD population is a more recently recognized phenomenon due to increasing life expectancy<sup>32,33</sup>. In this study, the elevated risk of ACS and ischemic stroke associated with ACHD despite adjustment for atherosclerotic risk factors suggests a non-atherosclerotic etiology of cardiovascular disease. The development of cardiovascular disease may be related to a number of other factors including surgical interventions<sup>34</sup>, physiological stressors of early life<sup>35</sup>, intrinsic cellular dysfunction, and genetic predisposition<sup>30</sup>. Risk for ischemic stroke and AF have previously been associated with septal defects (with or without closure) and palliative shunt procedures<sup>4,28,36</sup>, suggesting a cardioembolic rather than atherosclerotic mechanism. Indeed, our study exhibits a greater risk of ischemic stroke and AF among those with non-complex defects (comprised primarily of septal defects) compared to those with isolated AoV defects, supporting the existing literature. In individuals with repaired coarctation of the aorta, predisposition for CAD has been associated with endothelial dysregulation, increased intimal/medial thickness, and an inflammatory cytokine profile<sup>37</sup>, all of which may be intrinsic to the congenital anomaly itself or a result of surgical intervention. Mechanisms of intra-operative inflammation resulting in vascular injury mediated by cytokines such as TGF- $\beta$ 1 have been proposed but require further investigation<sup>38</sup>. While reports on the prevalence of CAD in adults with aortic valve malformations are variable<sup>39</sup>, bicuspid aortic valve has been associated with higher incidence of CAD than expected for age<sup>40</sup> and with underlying vasculopathies that predispose to CAD<sup>41</sup>. Variation at the *TEX41* locus discovered through genome-wide association study has recently been associated with both bicuspid aortic valve and CAD<sup>42</sup>, further underscoring the potential for a shared genetic basis of congenital heart malformations and acquired cardiovascular disease. Further investigation is necessary to delineate these potential mechanisms of cardiovascular disease unique to ACHD.

There are several strengths to this study. The data are derived from a large population-based cohort with comprehensive and uniformly collected data on all participants, irrespective of diagnosis of congenital heart disease, thereby decreasing potential detection bias. Additionally, the breadth of clinical data available in the UKB allowed us to define and



adjust for a range of sociodemographic, behavioral, and cardiometabolic potential confounding variables that were uniformly ascertained in ACHD and non-ACHD individuals alike. While the availability of baseline characteristics is greater than that available in most registry-based studies which often lack survey instruments, inclusion of covariates was restricted to cross-sectional data obtained at the time of enrollment (which occurred at different ages) thus potentially complicating interpretation. However, a sensitivity analysis assessing the potential bias introduced by time-static covariates showed no significant variation in results (Supplemental Table 7).

Our study shares limitations inherent to observational studies. As previously reported, the UKB is subject to a healthy volunteer bias<sup>43</sup> and includes individuals born during an earlier era of congenital heart disease. In the UK, the first complete repair for Tetralogy of Fallot performed in an infant occurred in the early 1960's, and with the UKB cohort born between 1931 and 1971, the majority of UKB participants predate the widespread availability of palliative procedures for complex ACHD. Thus, survivorship bias is also present as evidenced in the small number of ACHD participants classified as "complex" who were excluded from analysis. Furthermore, diagnoses and outcomes of interest managed only in an outpatient setting will not be well captured within the UKB or similar population-based registries<sup>44</sup>. As a result, our classification algorithm is primarily based upon hospital admission diagnoses which lack the specificity, sensitivity, and phenotypic detail available in institutional or practice-based ACHD registries<sup>45</sup>. While validation of our classification algorithm was limited by the inability to verify individual-level diagnoses with chart review, the sheer volume of control individuals for comparison dilutes any effects of false negative classifications of ACHD. Furthermore, while MRI was only available for 2% of all ACHD cases, visual inspection of available MRI data yielded a diagnostic positive predictive value of at least 91% (Supplemental Figure 2, supplemental media), providing a unique visual method of validation that is not possible in registry-based studies. Despite the limitations present, the classification algorithm ascertained a prevalence of ACHD of 4.2 per 1000 participants, which is reasonably within the range of previously published prevalence estimates ranging from 2.17 to 6.12 per 1000 adults<sup>10,46,47</sup>.

The potential for misclassification bias was most pronounced in the ascertainment of isolated AoV defects. Given the lack of a highly sensitive diagnostic code for congenital aortic valve malformations and the largely asymptomatic course in early life, the identification of these lesions is a challenge in any setting without imaging data. Although the majority of isolated AoV defects was inferred with non-imaging derived diagnostic information, we were able to increase our confidence in the classification through multiple sensitivity analyses (Supplemental Table 9–12) which demonstrated minimal changes in any estimates for cardiovascular outcomes. The roughly 1:1 ratio of isolated AoV defects to all other ACHD lesions as well as the predominance of men (68.9%) are also consistent with prior studies estimating the birth prevalence and sex ratio of bicuspid aortic valves<sup>48,49</sup>. While our classification algorithm does not allow for the identification of asymptomatic aortic valve defects, the literature suggests that most individuals with bicuspid aortic valves have acquired dysfunction by late adulthood<sup>3,50</sup>.

## Conclusion

In this analysis of ~500,000 British individuals from the UKB, we found a substantially higher burden of cardiovascular risk factors and disease incidence in individuals with lower complexity ACHD than in the general population. Furthermore, we estimated significant residual risk of adverse cardiovascular events associated with ACHD after adjusting for conventional cardiovascular risk factors. These findings highlight the importance for establishing long-term follow-up in patients with simple to moderately complex ACHD and the need for further study into the mechanisms of cardiovascular disease specific to this rapidly growing population of high-risk adults.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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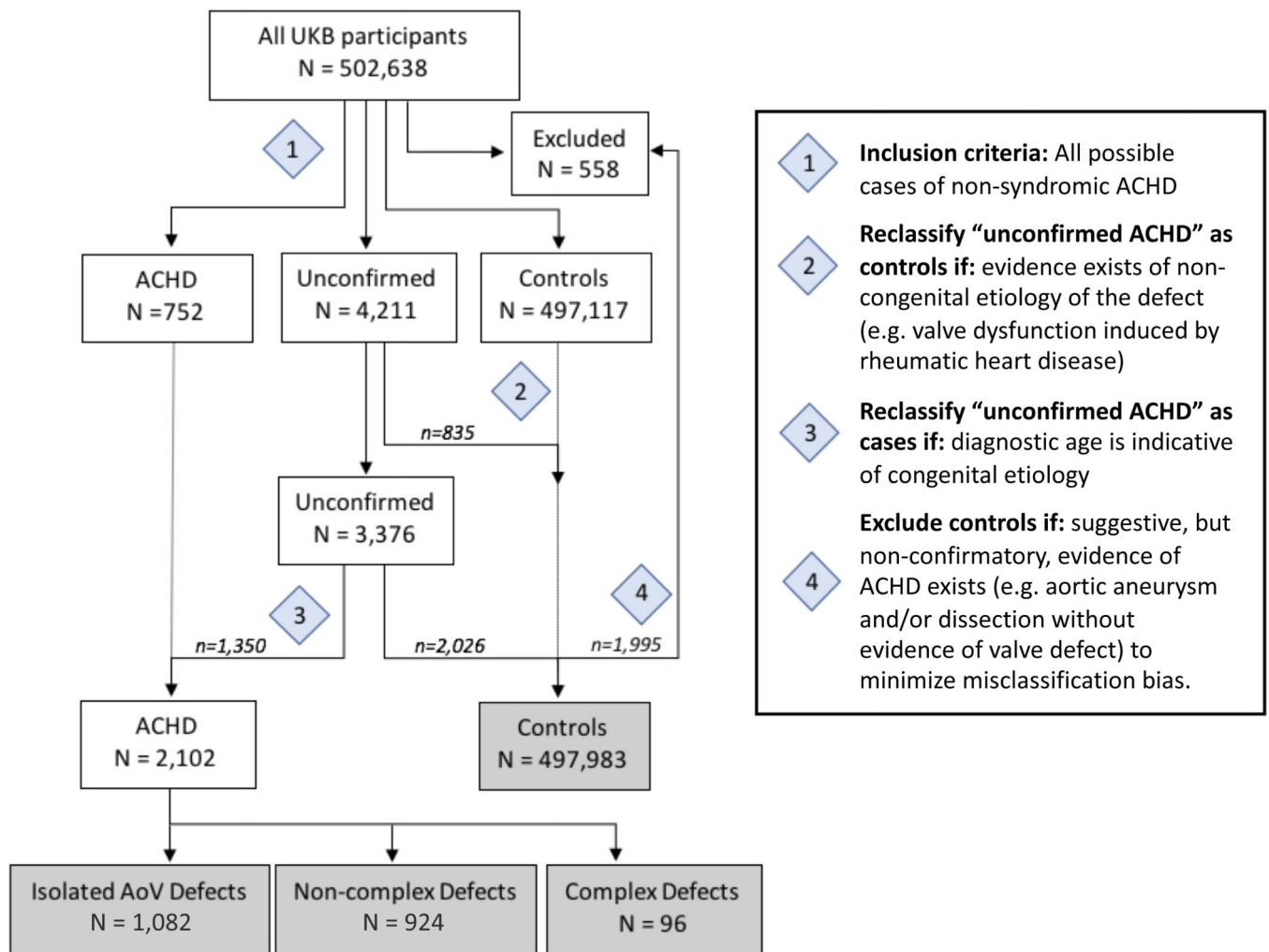
## Clinical Perspective

### What is new?

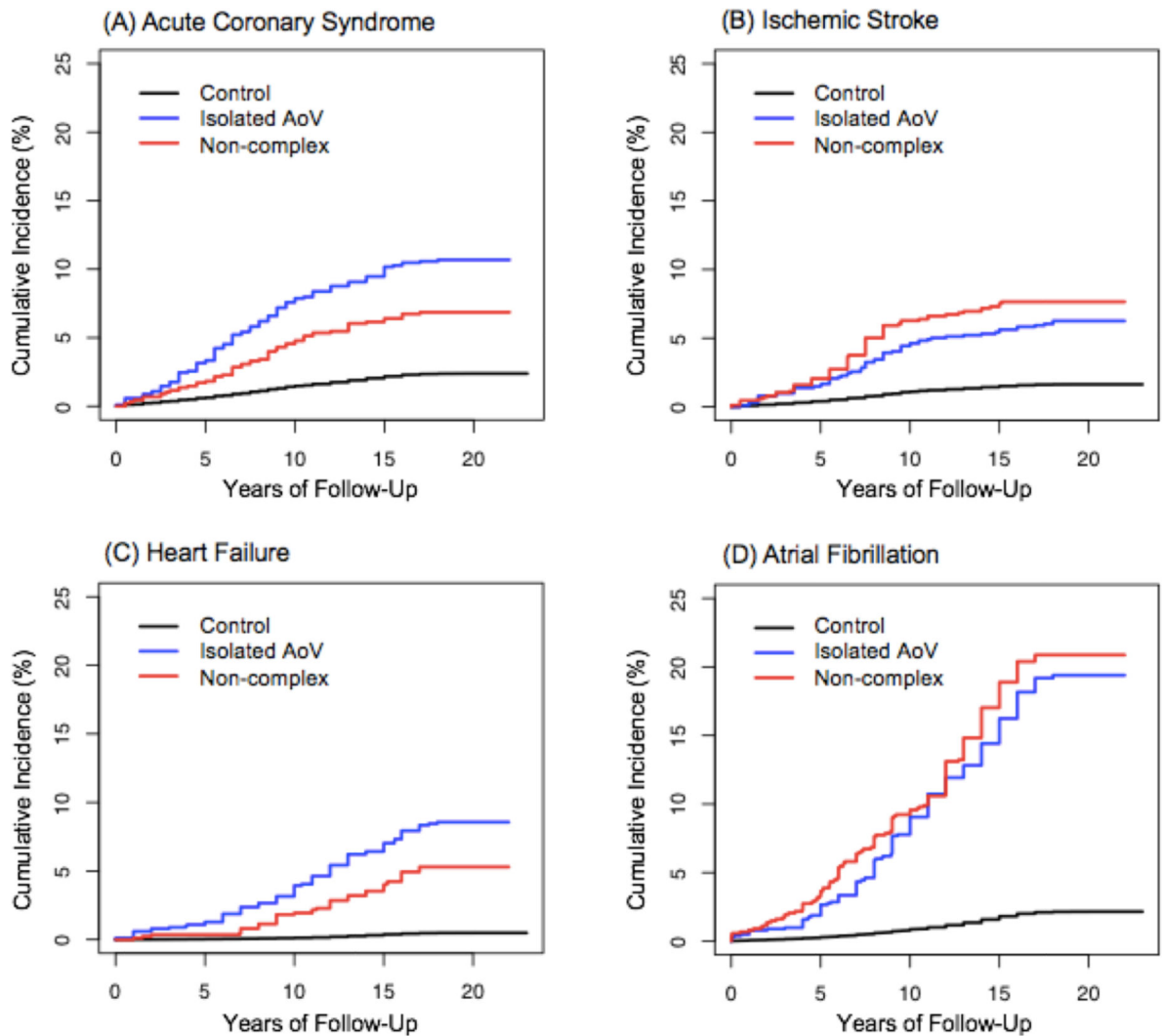
- This study quantifies the risk of cardiovascular morbidity directly attributable to lower complexity congenital heart disease.
- We identified 2,006 individuals with lower complexity congenital heart disease in the UK Biobank, a large prospective population-based cohort of over 500,000 individuals between 37 and 73 years of age with uniformly collected health information.
- Individuals with congenital heart disease had a higher burden of cardiovascular risk factors and incidence of adverse cardiovascular events as compared to the general population.
- After adjustment for conventional cardiovascular risk factors, the risk of adverse cardiovascular events remained 2 to 13 times higher in individuals with congenital heart disease.

### What are the clinical implications?

- Adults with “mild” congenital heart disease represent a large population of individuals previously considered to be at low risk for cardiovascular morbidity without need for long-term sub-specialized cardiovascular care.
- This study demonstrates that adults with lower complexity congenital heart disease are at significant risk of acquiring cardiovascular morbidities relative to the general population, highlighting the need for long-term surveillance and further research on prevention and risk mechanisms of acquired cardiovascular disease in this population.



**Figure 1.** Classification Algorithm Flowchart for Ascertaining Non-syndromic Adult Congenital Heart Disease (ACHD) in UK Biobank. Diagnostic codes (ICD9, ICD10, OPCS-4, and self-reported data) for defining case-control groups are given in Supplemental Tables 1–4. Individuals identified with complex defects were excluded from further analysis in this study.



No. at Risk	Years of Follow-Up				
	0	5	10	15	20
Control	491,706	485,535	475,509	461,082	128,382
Isolated AoV	1,016	941	796	668	175
Non-complex	878	815	692	584	170

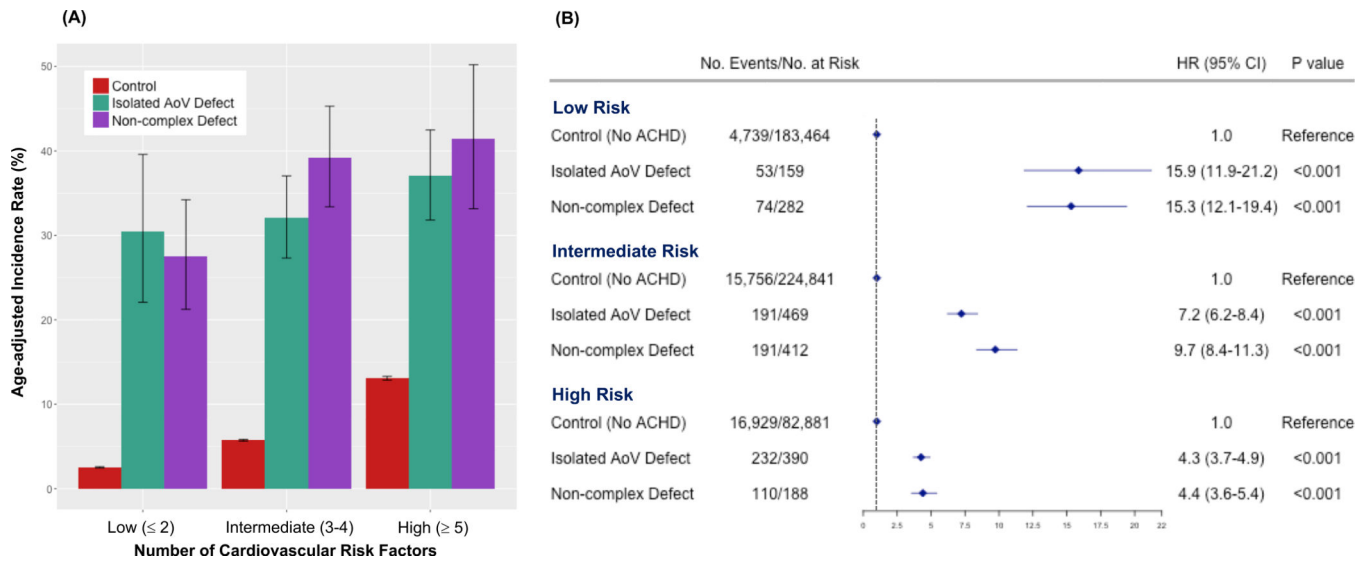
**Figure 2.**

Cumulative Incidence of Acute Coronary Syndrome, Ischemic Stroke, Heart Failure, and Atrial Fibrillation in Adults with Congenital Heart Disease Compared to General UKB Population

Panels A-D illustrate the unadjusted cumulative incidence of acute coronary syndrome, ischemic stroke, heart failure, and atrial fibrillation in individuals with isolated AoV defects, non-complex defects, and without ACHD (controls).

AoV = aortic valve; ACHD = adult congenital heart disease; No. = Number





**Figure 3.** Absolute and Relative Risk of MACE associated with ACHD Stratified by Number of Cardiovascular Risk Factors  
 (A) Age-Adjusted Absolute Incidence Rate of MACE Stratified by Number of Cardiovascular Risk Factors (B) Age-, Ethnicity-, Sex- and Townsend Deprivation Index-adjusted Cox Regression for MACE stratified by Number of Cardiovascular Risk Factors  
 ACHD = adult congenital heart disease; MACE = major adverse cardiovascular event; AoV = aortic valve; No. = Number; HR = hazard ratio

**Table 1.**

## Study Participant Characteristics at Enrollment

	CONTROL	ALL ACHD	ISOLATED AoV DEFECT	NON-COMPLEX	p value*
<b>n</b> <sup>†</sup>	497,983	2,006	1,082	924	
<b>Demographics</b>					
Age at Enrollment (median [IQR])	58 [50, 63]	58 [51, 63]	59 [53, 64]	57 [49, 63]	0.007
Male sex (%)	226,574 (45.5)	1,175 (58.6)	747 (69.0)	428 (46.3)	<0.001
Caucasian Ethnicity (%)	468,429 (94.2)	1,920 (95.9)	1,044 (96.8)	876 (94.8)	0.002
Townsend Deprivation Index (median [IQR])	-2.14 [-3.65, 0.54]	-1.74 [-3.39, 1.38]	-1.53 [-3.30, 1.49]	-1.92 [-3.44, 1.23]	<0.001
<b>Behavioral Risk Factors</b>					
Smoking (%)					<0.001
Never	271,321 (54.8)	982 (49.4)	468 (43.8)	514 (55.9)	
Current	52,473 (10.6)	223 (11.2)	133 (12.5)	90 (9.8)	
Former	171,277 (34.6)	782 (39.4)	467 (43.7)	315 (34.3)	
Alcohol consumption (%)					0.008
Seldom	152,844 (30.8)	666 (33.4)	322 (29.9)	344 (37.4)	
Daily	100,874 (20.3)	422 (21.1)	254 (23.6)	168 (18.2)	
Weekly	242,782 (48.9)	909 (45.5)	500 (46.5)	409 (44.4)	
Physical Activity (%)					0.067
High	245,532 (52.6)	924 (50.4)	509 (51.7)	415 (48.9)	
Low	221,486 (47.4)	909 (49.6)	476 (48.3)	433 (51.1)	
<b>Cardiometabolic Risk Factors</b>					
Positive Family History of CVD (%)	361,706 (74.4)	1,482 (75.7)	796 (75.3)	686 (76.1)	0.234
Systolic Blood Pressure (median [IQR])	137 [125, 150]	137 [125, 150]	139 [128, 152]	134 [121, 147]	0.566
Diastolic Blood Pressure (median [IQR])	82 [76, 89]	80 [73, 88]	81 [74, 88]	79 [73, 87]	<0.001
BMI (median [IQR])	26.7 [24.1, 29.9]	27.5 [24.7, 30.9]	27.8 [25.2, 31.4]	26.9 [24.2, 30.2]	<0.001
Obesity (%)	120,854 (24.4)	590 (29.8)	349 (32.7)	241 (26.4)	<0.001
Diagnosed/Treated for Hypertension (%)	272,727 (55.0)	1,361 (68.8)	824 (77.4)	537 (58.9)	<0.001
Diagnosed/Treated for Hyperlipidemia (%)	92,536 (18.7)	811 (41.1)	538 (50.6)	273 (29.9)	<0.001
Diagnosed/Treated for Diabetes (%)	18,709 (3.8)	135 (6.7)	95 (8.8)	40 (4.3)	<0.001

ACHD = adult congenital heart disease, AoV = aortic valve, CVD = cardiovascular disease, BMI = body mass index, IQR = interquartile range

\* P values given for comparison between Controls and All ACHD.

<sup>†</sup>Number of participants do not sum to group totals due to missing values.

**Table 2.**

Multivariable-Adjusted Hazard Ratios for Cardiovascular Events in Adults with Congenital Heart Disease

	No. Events/No. At Risk <sup>‡</sup>	Unadjusted <sup>*</sup>		Adjusted <sup>†</sup>	
		HR (95% CI)	P value	HR (95% CI)	P value
<b>Acute Coronary Syndrome (ACS)</b>					
Controls (No ACHD)	11,666/491,706	1	ref	1	ref
Isolated AoV defects	108/1,016	3.9 (3.2–4.7)	<10 <sup>-16</sup>	2.1 (1.7–2.5)	1.5 × 10 <sup>-11</sup>
Non-complex defects	60/878	3.7 (2.9–4.8)	<10 <sup>-16</sup>	2.0 (1.5–2.8)	8.7 × 10 <sup>-6</sup>
<b>Ischemic Stroke</b>					
Controls (No ACHD)	7,991/491,706	1	ref	1	ref
Isolated AoV defects	63/1,016	3.7 (2.9–4.8)	<10 <sup>-16</sup>	2.2 (1.7–2.9)	1.3 × 10 <sup>-8</sup>
Non-complex defects	67/878	6.0 (4.7–7.6)	<10 <sup>-16</sup>	5.1 (3.9–6.6)	<10 <sup>-16</sup>
<b>Heart Failure (HF)</b>					
Controls (No ACHD)	2,333/491,706	1	ref	1	ref
Isolated AoV defects	86/1,016	17.9 (14.4–22.3)	<10 <sup>-16</sup>	12.2 (9.5–15.6)	<10 <sup>-16</sup>
Non-complex defects	46/878	16.1 (12.0–21.6)	<10 <sup>-16</sup>	13.0 (9.4–18.1)	<10 <sup>-16</sup>
<b>Atrial Fibrillation (AF)</b>					
Controls (No ACHD)	1,810/491,706	1	ref	1	ref
Isolated AoV defects	195/1,016	9.1 (7.9–10.5)	<10 <sup>-16</sup>	7.5 (6.4–8.7)	<10 <sup>-16</sup>
Non-complex defects	182/878	14.1 (12.2–16.3)	<10 <sup>-16</sup>	13.0 (11.1–15.2)	<10 <sup>-16</sup>

\* Adjusted for sociodemographic factors (age at enrollment, sex, ethnicity, and Townsend Deprivation Index).

† Adjusted for sociodemographic factors as in Unadjusted models, plus cardiovascular risk factors (smoking status, alcohol consumption, physical activity, family history of cardiovascular disease, body mass index, systolic and diastolic blood pressure adjusted for use of anti-hypertensive medication, hyperlipidemia, diabetes).

‡ "No. At Risk" reflects total number of participants with non-missing values for event within pre-determined follow-up time.

ACHD = adult congenital heart disease; AoV = aortic valve; HR = hazard ratio