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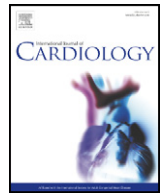
Short communication

Risk of coronary artery disease in adults with congenital heart disease: A comparison with the general population

Joey M. Kuijpers [a,b,1], Ilonca Vaartjes [c,1], Jouke P. Bokma [a,b,1], Joost P. van Melle [d,1], Gertjan Tj Sieswerda [e,1], Thelma C. Konings [f,1], Mirjam Bakker-de Boo [g,1], Ivo van der Bilt [h,1], Bart Voogel [i,1], Aeilko H. Zwinderman [j,1], Barbara J.M. Mulder [a,b,1], Berto J. Bouma [a,*,1]

[a] Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands
[b] Netherlands Heart Institute, Utrecht, the Netherlands
[c] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands
[e] Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
[f] Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands
[g] Department of Cardiology, Gelre Ziekenhuis, Apeldoorn, the Netherlands
[h] Department of Cardiology, HagaZiekenhuis, Den Haag, the Netherlands
[i] Department of Cardiology, Spaarne Gasthuis, Haarlem/Hoofddorp, the Netherlands
[j] Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, the Netherlands

ABSTRACT

Background: Coronary artery disease (CAD) will increasingly determine outcome in the aging adult congenital heart disease (CHD) population. We aimed to determine sex-specific incidence of CAD in adult CHD patients throughout adulthood, compared to the general population.
Methods and results: We followed 11,723 adult CHD patients (median age 33 years; 49% male; 57% mild, 34% moderate, 9% severe CHD) from the Dutch CONCOR registry, and two age-sex-matched persons per patient from the general population for first CAD event in national registers (period 2002–2012). Incidence rates were estimated using smoothed hazard functions. CAD risk during follow-up, stratified by CHD severity, was compared using proportional subdistribution hazards regression. In ACHD patients, 103 CAD events (43 women) occurred over 60,456 person-years. Rates per 1000 person-years increased from 0.3 (95% confidence interval: 0.1–0.6) at age 20 to 5.8 (3.7–8.9) at 70 years in female, and from 0.5 (0.3–1.0) to 7.8 (5.1–11.8) in male patients. Compared to the general population, relative risk was 12.0 (2.5–56.3) in women and 4.6 (1.7–12.1) in men aged 20 years. Relative risk declined with age, remaining significant up to age ~65 years in women and ~50 years in men. In patients with mild, moderate and severe CHD, CAD risk was 1.3 (0.9–1.9), 1.6 (1.0–2.5) and 2.9 (1.3–6.9) times increased compared to the general population, respectively.
Conclusions: We found increased CAD risk in adult CHD patients, with greater relative risk at younger age, in women and those with more severe CHD. These results underline the importance of screening for and treatment of CAD risk factors in these patients.

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1. Introduction

In the aging adult congenital heart disease (ACHD) population, prognosis is increasingly determined by acquired coronary artery disease (CAD) [1–3]. Thus, it is important to determine CAD incidence in ACHD patients. Recent population-based CHD studies reported increased incidence of ischemic heart disease in children and adults with CHD [4–6]. No studies have yet reported sex- and age-specific CAD incidence rates from early to late adulthood; we aimed to determine this, and CHD-severity specific cumulative CAD incidence, in ACHD patients compared to the general population.

2. Methods

The study conforms to the Declaration of Helsinki, and was approved by the ethics boards of participating centres.

2.1. Study population and data collection

We linked the Dutch nationwide CONCOR ACHD registry, Hospital Discharge Register (HDR) and Cause of Death Register (CDR) through Statistics Netherlands.

Since 2002, ACHD patients ≥ 18 years are included in CONCOR from secondary and tertiary referral centres. CHD diagnoses and comorbidities are obtained from medical records. In patients with multiple CHDs, the most severe lesion (Supplemental table I) is designated the primary CHD. The HDR and CDR contain person-linked discharge records of hospital admissions (including International Classification of Diseases, ninth revision [ICD-9]-coded diagnoses), and ICD-10-coded causes of deaths in Dutch citizens (according to compulsory notifications of cause of death by treating physicians or pathologists), respectively.

CONCOR was linked to the Population Register (PR; registry of all Dutch citizens) using postal code (4 digits, 2 letters), sex and birthdate as the linkage key. Linkage-key unique persons are unique in the CDR. In the HDR, linked to the PR using *partial* (4-digit) postal code, sex and birthdate, PR-unique persons may lose linkage-key unicity. We selected 11,723 ACHD patients without prior myocardial infarction from CONCOR (ACHD cohort), and two sex-age-matched persons from the PR per ACHD patient (general population cohort), uniquely identified in CDR *and* HDR anywhere between January 2002 and December 2012.

Primary CHD lesion was obtained from CONCOR, and categorized into severe, moderate and mild, as previously described (definitions: Supplemental table I).[s1,2] The outcome was hospital admission for acute coronary syndrome (ICD-9 410, 411.1) or death caused by CAD (ICD-10 I20.0/.1/.8/.9, I21, I22, I25.0/.1/.5-.9). We audited medical records for all HDR-registered CAD admissions of CONCOR patients in our centre during the study-period (*n* = 16). In 88% the diagnosis was correct (Supplemental table II), in accordance with European Society of Cardiology criteria.[s4,5]

2.2. Statistical analysis

Subjects were followed from inclusion to first CAD, or censored at non-CAD-related death, emigration, loss of unique HDR identification or end-of-study (December 31st 2012). Age-specific incidence rates were estimated using smoothed estimates of the hazard function [7]. Differences between cohorts were calculated from these estimates. Crude incidence rates were compared using Poisson regression.

Cumulative incidence functions were constructed per CHD category, proportional subdistribution hazards regression analysis was used to compare rates with matched general-population subjects, using non-CAD-related death as the competing event. Subdistribution hazard ratios (sdHRs), 95% confidence intervals (95%CIs) and *p*-values are reported.

Analyses were performed using *R* v3.3.1 (R Foundation, Vienna, Austria) and SPSS v23 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Supplemental table III shows characteristics of the ACHD patients; 6622 (56.5%), 4014 (34.2%) and 1087 (9.3%) had mild, moderate and severe CHD, respectively. Percentage males (overall: 48.8%) and median age at inclusion (overall: 32.9 years, interquartile range: 23.0–45.7) differed between mild (male: 45.5%; age: 36.1, 24.9–48.7), moderate (52.1%; 31.3, 22.3–43.6) and severe (56.9%; 23.5, 19.8–30.8) CHD (*p* < 0.001, all pairwise comparisons). Mean follow-up: 5.2 ± 3.1 years.

3.2. Incidence rates, compared with general population

In ACHD patients, 103 CAD cases (79[77%] admissions, 24 deaths) occurred over 60,456 person-years, 60 cases in men (45[75%]

admissions) and 43 (34[79%] admissions) in women. Fig. 1 shows estimated CAD incidence rates. Rates per 1000 person-years increased from 0.3(95%CI = 0.1–0.6) at age 20 to 5.8(3.7–8.9) at 70 years in female, and from 0.5(0.3–1.0) to 7.8(5.1–11.8) in male patients (95%CIs for estimates in Fig. 1: Supplemental Fig. I).

First CAD occurred at younger age in ACHD patients compared to the general population (52.4 ± 15.1 vs 60.0 ± 12.6 years, *p* < 0.001). Fig. 2 shows absolute and relative incidence-rate differences, in ACHD compared to the general population: incidence was significantly increased up to age ~65 years in women, and ~50 years in men. Small absolute differences compared to the general population (age 20, women: 0.2/1000person-years[95%CI = 0.0–0.5], men: 0.4[0.0–0.8]) constituted the greatest hazard ratio (HR) in early adulthood (age 20, women: HR = 12.0[95%CI, 2.5–56.3], men: 4.6[1.7–12.1]).

Supplemental table IV shows numbers of cases, person-time at risk and crude incidence rates per cohort.

3.3. Cumulative incidence during follow up by CHD category

At 10-year follow-up, cumulative CAD incidence was 1.4%(95%CI = 0.9–1.8), 1.9%(1.2–2.6) and 1.9%(0.8–3.0) in mild, moderate and severe CHD, respectively. Compared to the general population, the sdHR was 1.3(95%CI = 0.9–1.9, *p* = 0.136), 1.6(1.1–2.5, *p* = 0.026) and 2.9 (1.3–6.9, *p* = 0.013), respectively (cumulative incidence curves: Supplemental fig. II).

4. Discussion

We found increased CAD risk in ACHD patients compared to the general population. Small absolute risk-increases constituted considerable relative risks at young age (12.0 and 4.6 in women and men aged 20 years, respectively). CAD rates were higher in men throughout adulthood, but increased up to older age in women and remarkably lower than in the general population in older men (statistically non-significant). Cumulative CAD incidence was not significantly increased in mild, but ~2 and ~3 times increased in moderate and severe CHD, respectively.
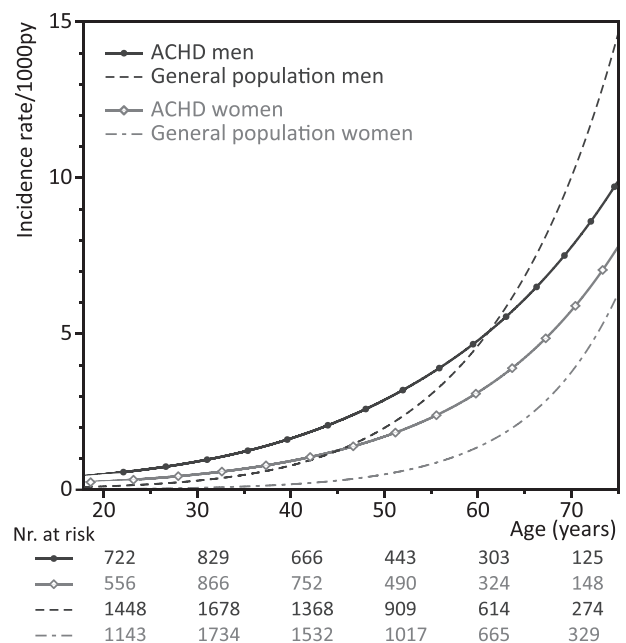

Fig. 1. Incidence rates of coronary artery disease by age and sex. Estimated sex-specific incidence rates of CAD, in cases per 1000 person-years, during adulthood in the ACHD and general population cohorts. 95% confidence intervals for all estimates are found in Supplemental Fig. I. Abbreviations: ACHD, adult congenital heart disease; py, person-years.
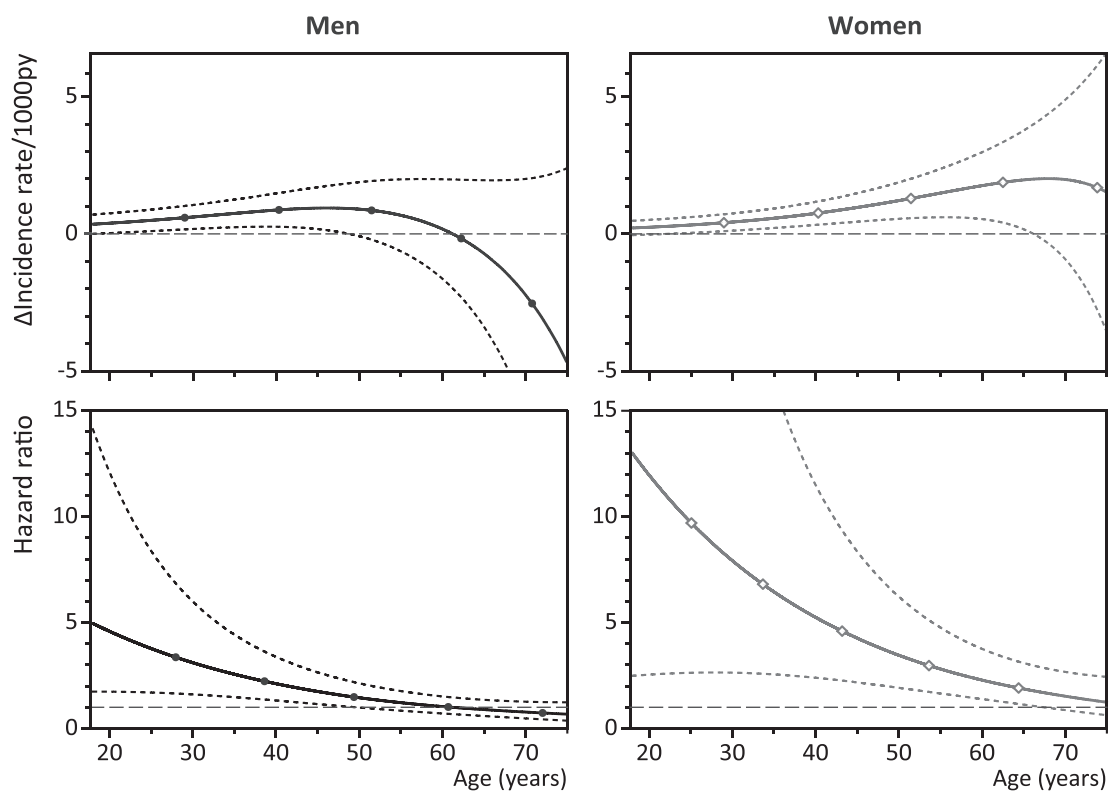
Fig. 2. Differences in incidence rates of coronary artery disease by age, in men and women with congenital heart disease compared to the matched general population cohort. Absolute differences in CAD rates (in cases per 1000 person-years), in the ACHD compared to the general population cohort are shown in the upper panels for men (left panel) and women (right panel) separately. Relative differences (hazard ratios) are likewise shown in the lower panels. In each panel, the solid line (black with solid dots for men, grey with open squares for women, conform Fig. 1) represents the estimated absolute/relative risk difference; the dashed lines represent the upper and lower bounds of the 95% confidence interval for each estimate. Abbreviations: py, person-years.

A Swedish study also found increased ischemic-heart-disease rates in paediatric/young adult CHD patients [6], and Danish [4] and English [5] studies found increased myocardial infarction/acute coronary syndrome rates in older patients. Moreover, the Swedish and Danish studies also found greater relative risk in more severe CHD; the latter also reported greater relative risk in women. Contrary to present results, the Swedish and English studies reported increased risk in simple (mild) CHD [5,6]. Importantly, different outcome-definitions, CHD categorizations and populations complicate comparisons.

CAD in ACHD is probably caused by an interaction between conventional cardiovascular risk factors [8] and predisposing CHD-related factors, including coronary anomalies and endothelial dysfunction [9–11]. CHD-related aetiology probably underlays increased risk in early adulthood, before conventional risk factors likely cause significant atherosclerosis. Indeed, young CHD patients with ischemic heart disease from the Swedish registry had proportionately fewer conventional risk factors than general-population controls [6]. However, the English study in older ACHD patients (median age 58 years) found increased CAD risk adjusted for conventional risk factors, indicating a contribution of CHD-related factors [5].

With advancing age, conventional risk factors may increasingly determine CAD risk: in an ACHD case-control study (mean age 55 years), CAD was associated with conventional (not CHD-related) risk factors [8]. Moreover, ≥1 conventional risk factor is present in 70–80% of ACHD patients [12,13], and increased rates of smoking [5], hypertension [5,13,14], diabetes [5,14,15] and metabolic syndrome [16] have been reported.

The greater risk-increase in – relatively young – patients with severe CHD could be explained by higher prevalence of CHD-related risk factors in these patients, including anomalous coronary anatomy. Indeed, transposition of the great arteries is associated with (post-surgical)

coronary abnormalities and increased CAD risk [10], and other severe CHDs are associated with high prevalence of coronary anomalies [11]. Widespread endothelial dysfunction in cyanotic CHD may potentiate premature CAD [17]. Moreover, patients with severe CHD may have worse atherosclerotic risk-profiles, suggested by lower physical activity levels [18] and higher diabetes risk [15].

No available data explains the greater CAD risk-increase in women than in men with CHD. Hypothetically, sex-differences in conventional cardiovascular risk in the general population (e.g. more smoking, hypercholesterolemia and hypertension in men) [19] may be less pronounced in ACHD [13]. Alternatively, sex-differences in conventional risk factors may be less consequential if risk is predominantly determined by CHD-associated factors. That risk fell below general-population risk in older men may be explained by higher early CHD-associated mortality in men, and lower prevalence of (CHD-associated) risk factors in the surviving elderly patients [6]. Future studies should determine whether these observations are reproducible in other cohorts.

Merits of this study are the nationwide, prospectively followed ACHD cohort, and uniformly collected data from reliable population-based registries. HDR codes for ACS were valid in ACHD patients upon medical-record review. A previous study found high positive predictive values of the HDR for myocardial infarction (97%) and unstable angina (78%); sensitivity was high for myocardial infarction (84%) but rather low for unstable angina (53%), incidence of which may thus be underestimated [20]. Absolute incidences may be further underestimated: the percentage missing records in the HDR increased between from 2005 and 2012 (3.3% to 24.7%), due to decline in participating hospitals. Any underestimation is unlikely differential between the cohorts, and thus unlikely to affect estimated risk-differences. Data on conventional cardiovascular risk-factors were not available, limiting insight into the mechanisms behind the observed risk-differences and

identification of targets for intervention. Analyses for specific CHD types were not performed: privacy restrictions from the Central Bureau of Statistics prohibit reporting small-group data.

In conclusion, we found increased CAD risk in ACHD patients, with greater relative risk at younger age, in women and those with more severe CHD. These findings underline the importance of screening for and treatment of conventional risk factors in these patients from a young age. To aid this practice, future research should identify the mechanisms underlying CAD in specific CHD types, and the observed sex-specific risk-increases.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.11.114.

References

[1] P. Khairy, R. Ionescu-Ittu, A.S. Mackie, M. Abrahamowicz, L. Pilote, A.J. Marelli, Changing mortality in congenital heart disease, J. Am. Coll. Cardiol. 56 (2010) 1149–1157.

[2] P. Pillutla, K.D. Shetty, E. Foster, Mortality associated with adult congenital heart disease: trends in the US population from 1979 to 2005, Am. Heart J. 158 (2009) 874–879.

[3] O. Tutarel, A. Kempny, R. Alonso-Gonzalez, R. Jabbour, W. Li, A. Uebing, K. Dimopoulos, L. Swan, M.A. Gatzoulis, G.-P. Diller, Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality, Eur. Heart J. 35 (2014) 725–732.

[4] M. Olsen, B. Marino, J. Kaltman, H. Laursen, L. Jakobsen, W. Mahle, G. Pearson, N. Madsen, Myocardial infarction in adults with congenital heart disease, Am. J. Cardiol. 120 (2017) 2272–2277.

[5] P. Saha, P. Potiny, J. Rigdon, M. Morello, C. Tcheandjieu, A. Romfh, S.M. Fernandes, D.B. McElhinney, D. Bernstein, G.K. Lui, G.M. Shaw, E. Ingelsson, J.R. Priest, Substantial cardiovascular morbidity in adults with lower-complexity congenital heart disease, Circulation 139 (2019) 1889–1899.

[6] M. Fedchenko, Z. Mandalenakis, A. Rosengren, G. Lappas, P. Eriksson, K. Skoglund, M. Dellborg, Ischemic heart disease in children and young adults with congenital heart disease in Sweden, Int. J. Cardiol. 248 (2017) 143–148.

[7] P. Rebora, A. Salim, Reilly M. bshazard: a flexible tool for nonparametric smoothing of the hazard function, R J 6 (2014) 114–122.

[8] J.P. Bokma, I. Zegstroo, J.M. Kuijpers, T.C. Konings, R.R.J. van Kimmenade, J.P. van Melle, P. Kiès, B.J.M. Mulder, B.J. Bouma, Factors associated with coronary artery disease and stroke in adults with congenital heart disease, Heart Br Card Soc 104 (2018) 574–580.

[9] G.K. Lui, S. Fernandes, D.B. McElhinney, Management of cardiovascular risk factors in adults with congenital heart disease, J. Am. Heart Assoc. 3 (2014) https://doi.org/10.1161/JAHA.114.001076e001076.

[10] A. Legendre, J. Losay, A. Touchot-Koné, A. Serraf, E. Belli, J.D. Piot, V. Lambert, A. Capderou, C. Planche, Coronary events after arterial switch operation for transposition of the great arteries, Circulation 108 (Suppl. 1) (2003) II186–190.

[11] F. Yu, B. Lu, Y. Gao, Z. Hou, U.J. Schoepf, J.V. Spearman, H. Cao, M. Sun, S. Jiang, Congenital anomalies of coronary arteries in complex congenital heart disease: diagnosis and analysis with dual-source CT, J Cardiovasc Comput Tomogr 7 (2013) 383–390.

[12] G.K. Lui, I.S. Rogers, V.Y. Ding, H.K. Hedlin, K. MacMillen, D.J. Maron, C. Sillman, A. Romfh, T.C. Dade, C. Haeffele, S.R. Grady, D.B. McElhinney, D.J. Murphy, S.M. Fernandes, Risk estimates for atherosclerotic cardiovascular disease in adults with congenital heart disease, Am. J. Cardiol. 119 (2017) 112–118.

[13] P. Moons, K. Van Deyk, D. Dedroog, E. Troost, W. Budts, Prevalence of cardiovascular risk factors in adults with congenital heart disease, Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol 13 (2006) 612–616.

[14] J. Billett, M.R. Cowie, M.A. Gatzoulis, I.F. Vonder Muhll, A. Majeed, Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis, Heart Br Card Soc 94 (2008) 1194–1199.

[15] Madsen NL, Marino BS, Woo JG, Thomsen RW, Videbœk J, Laursen HB, Olsen M. Congenital heart disease with and without cyanotic potential and the long-term risk of diabetes mellitus: a population-based follow-up study. J. Am. Heart Assoc. 2016;5.

[16] J.F. Deen, E.V. Krieger, A.E. Slee, A. Arslan, D. Arterburn, K.K. Stout, M.A. Portman, Metabolic syndrome in adults with congenital heart disease, J. Am. Heart Assoc. 5 (2016).

[17] R.L. Cordina, S. Nakhla, S. O'Meagher, J. Leaney, S. Graham, D.S. Celermajer, Widespread endotheliopathy in adults with cyanotic congenital heart disease, Cardiol. Young 25 (2015) 511–519.

[18] J.S. Dua, A.R. Cooper, K.R. Fox, S.A. Graham, Physical activity levels in adults with congenital heart disease, Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol 14 (2007) 287–293.

[19] P. Jousilahti, E. Vartiainen, J. Tuomilehto, P. Puska, Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland, Circulation 99 (1999) 1165–1172.

[20] A.H.H. Merry, J.M.A. Boer, L.J. Schouten, E.J.M. Feskens, W.M.M. Verschuren, A.P.M. Gorgels, Brandt PA van den. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study, Eur. J. Epidemiol. 24 (2009) 237–247.