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Survivorship in Children and Young Adults With Congenital Heart Disease in Sweden

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IMPORTANCE Mortality in patients with congenital heart disease (CHD) has markedly decreased during recent decades because of advancement in pediatric care. However, there are limited data on survival trends in children and young adults with CHD compared with the general population.

OBJECTIVE To determine survivorship in children and young adults with CHD compared with matched controls.

DESIGN, SETTING, AND PARTICIPANTS A registry-based, prospective, matched-cohort study was conducted in Sweden. Data from the national patient and cause of death registers were linked to identify individuals with CHD born between January 1, 1970, and December 31, 1993, who were registered at or after birth. Follow-up and comorbidity data were collected until December 31, 2011. Survival analyses were performed with the Cox proportional hazards model; these analyses were performed from January 1, 1970, to December 31, 2011. A total of 21 982 patients with CHD in Sweden were identified. The mean (SD) follow-up time was 27.0 (8.86) years. Children serving as controls (n = 219 816) (10 for each patient), matched for birth year, sex, and county, were randomly selected from the general population.

MAIN OUTCOMES AND MEASURES Survivorship in young patients with CHD and controls.

RESULTS Of the 21 982 patients who were born between 1970 and 1993 and were registered with the diagnosis of CHD, 10 650 were female (48.4%). Median age at index registration was 4.22 years (interquartile range, 17.07 years). Survivorship among children younger than 5 years was increased from 96% in those born in 1970-1979 to 98% in those born in 1990-1993. Hazard ratios (HRs) of death in relation to that in control individuals decreased from 225.84 (95% CI, 136.84-372.70) to 33.47 (95% CI, 22.54-49.70). A substantial, but less pronounced, absolute and relative increase in survivorship was found in older patients (HRs ranged from 24.52; 95% CI, 11.72-51.26, at 5-9 years to 4.27; 95% CI, 2.29-7.95, at 18-29 years). According to a hierarchical CHD classification, the group of patients with the most severe complex defects (ie, common arterial trunk, transposition of the great vessels, double inlet ventricle, hypoplastic left heart syndrome, tetralogy of Fallot, and atrioventricular septal defect) had the highest risk for death (HR, 64.07; 95% CI, 53.39-76.89).

CONCLUSIONS AND RELEVANCE Despite substantially increasing absolute and relative survivorship in children and young adults with CHD, the mortality risk remains high compared with the risk in matched controls. Further research on reducing the death rate in this vulnerable group is required.

Supplemental content

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Congenital heart disease (CHD) is one of the most common types of birth defects present in approximately 1% of children born alive, and there has been an increase in the prevalence of CHD over the past decade as a consequence of improved care.[1-5] Several studies have shown a reduction in the rate of death from CHD with improvement in pediatric care and surgical techniques.[6-15] However, patients with CHD still have a markedly high death rate, and CHD remains one of the major causes of death during infancy and childhood.[9,16,17] A recent report showed that there were more than 200 000 deaths related to CHD globally, of which most occurred in young patients.[16] However, a recent study from Europe reported a relatively low mortality rate (2.8%) in young adults with 1 of 8 of the most common CHD diagnoses during 5 years of follow-up,[18] but reports have been conflicting.[19] According to a recently published Danish registry study, even patients with simple CHD that was diagnosed between 1948 and 1973 and who were alive at age 15 years had a higher rate of mortality during long-term follow-up compared with the general population.[20]

As a group, patients with CHD display considerable heterogeneity and complexity. However, small numbers of patients with CHD in previous studies have limited the possibility to evaluate subgroups separately.

We investigated age- and birth cohort-specific trends in absolute and relative mortality in individuals with CHD who were born between 1970 and 1993 and compared them with controls. We used the hierarchical categorization of heart malformations published in 2007 by Marelli et al[21] combined with large nationwide Swedish registries. The purpose of our study was to investigate survivorship in children and young adults with CHD compared with matched population controls.

Key Points

Question Has survivorship in young children with congenital heart disease increased in Sweden?

Finding A registry-based, prospective, matched-cohort study showed that, among children younger than 5 years, survivorship was increased in those born at the beginning of 1990 compared with children born in the 1970s; however, the overall mortality risk was higher, depending on the complexity of the disease, than in matched controls.

Meaning Absolute and relative survivorship increased substantially, but mortality remains high in young patients with congenital heart disease compared with matched controls, particularly in subsets of children with complex issues.

Methods

Study Population and Design

Data from the Swedish National Patient Register were collected to identify patients with a diagnosis of any type of CHD.[22] All diagnoses were coded according to the *International Classification of Diseases, Eighth Revision*; *International Classification of Diseases, Ninth Revision*; and *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision* (ICD).

The study was approved by the Gothenburg Regional Research Ethics Board with need for informed consent waived. All national registration numbers were replaced with a code in the final data set by the Swedish National Board of Health and Welfare.

We identified 21 982 patients who were born between January 1970 and December 1993 with the diagnosis of CHD and who were registered at any time in the Swedish National Hospital Inpatient Register, including inpatient data (complete since 1987, but with coverage of all hospitals performing thoracic surgery since 1970), and National Hospital Outpatient Register data (complete since 2001). Follow-up and comorbidity data were collected at inclusion in the study (first registration of CHD diagnosis) ending on December 31, 2011, or death. In our study, 2.6% of all cases and 3.0% of all controls emigrated during the study. The median age at index registration was 9.6 years (range, 4.2-26.5 years); 75.9% were identified by the National Hospital Inpatient Register and 23.5% by the National Hospital Outpatient Register.

Each patient with CHD was matched by birth year, sex, and county with 10 control individuals without the diagnosis of CHD obtained from the Total Population Register in Sweden.[23] Only 9 controls were available for 73 patients with CHD. We used a hierarchical CHD categorization to classify CHD patients into 5 groups according to lesions.[21] With this categorization, group 1 was defined as patients with the diagnosis of a common arterial trunk, transposition of the great vessels, double inlet ventricle, hypoplastic left heart syndrome, tetralogy of Fallot, or atrioventricular septal defect. Group 2 was defined as patients with atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, or Ebstein anomaly. Group 3 was defined as patients with the diagnosis of unspecified congenital malformations of the cardiac septum. Group 4 was defined as patients with the diagnosis of congenital malformations of the pulmonary artery, congenital malformations of the pulmonary valve, congenital malformations of the tricuspid valve, congenital malformations of the aortic valve, congenital malformations of the mitral valve, or congenital malformations of the great veins. Group 5 was defined as patients with the diagnosis of other unspecified congenital malformations of the aorta, other specified and unspecified congenital malformations of the heart, or unspecified congenital malformations of the circulation.

Definitions

The ICD codes for each diagnosis that was registered between 1970 and 2011 are presented in eTable 1 in the Supplement. Patients with CHD were considered any patient with at least 1 outpatient visit, 1 hospital discharge, or a death certificate with a registered diagnosis of CHD. Operations on the cardiovascular system were classified as codes 30-32 (classification of operations in Swedish, 6th version)[24] or F codes (classification of surgical procedures in Swedish, version 1.9).[25] The postoperative period was defined as the 30-day period after the operation or intervention date. Mortality due to cardiovascular

Table 1. Mortality Risk in Overall Patients and 5 Groups of Lesions in Patients With CHD Compared With Matched Controls

Categorical Hierarchy CHD Group[a]	No. of Deaths in Patients With CHD/Total No. of Patients With CHD (%)	No. of Deaths in Controls/Total No. of Controls (%)	HR for Mortality (95% CI)[b]
Group 1	754/3077 (24.5)	142/30 780 (0.5)	64.07 (53.39-76.89)
Group 2	527/10 821 (4.9)	505/108 208 (0.5)	10.9 (9.65-12.32)
Group 3	63/473 (13.3)	30/4730 (0.6)	21.74 (14.06-33.61)
Group 4	111/3206 (3.5)	135/32 059 (0.4)	8.53 (6.63-10.99)
Group 5	218/4404 (5.0)	265/44 039 (0.6)	10.42 (7.58-14.44)
All CHD	1673/21 982 (7.6)	1077/219 816 (0.5)	16.51 (15.29-17.83)

Abbreviations: CHD, congenital heart disease; HR, hazard ratio.

[a] The CHD groups are defined in the Study Population and Design subsection of the Methods section.

[b] All $P < .001$.

disease was defined as codes 390 to 458 (*ICD-8*), 390 to 459 (*ICD-9*), or I00 to I99 (*ICD-10*).

Statistical Analysis

Descriptive statistics are presented for demographic data, and comorbidities are shown for the study population. Mortality hazard ratios (HRs) with 95% CIs for comparing cases with matched controls were estimated by means of the stratified Cox proportional hazards model. Strata were defined by sex, birth year, and county. For the time scale in our survival analyses, we used age attained within the study. Cases and controls were matched from time of birth and followed-up until death, emigration, or end of the study. Kaplan-Meier curves with 95% CIs were plotted, and we compared cases with controls, in total and within groups, from birth during long-term follow-up. We also used the time-to-event Cox proportional hazards model when analyzing only cases to estimate HRs for covariates. Two-sided *P* values were used, with $P < .05$ considered statistically significant. Data analysis was conducted from January 1, 1970, to December 31, 2011. SAS, version 9.4 (SAS Institute Inc) and R, version 3.1 (R Foundation for Statistical Computing) were used to perform all statistical analyses.

Results

We identified 21 982 patients who were born between 1970 and 1993 and were registered with the diagnosis of CHD (including 10 650 females [48.4%]). Median age at index registration was 4.22 years (interquartile range, 17.07 years). We included 219 816 matched controls. The characteristics of our study population are reported in eTable 2 in the Supplement. More than 90% of the patients with CHD and the controls were born in Sweden.

By the end of the study period, 1673 patients with CHD and 1077 controls had died, with a mean (SD) follow-up of 27.0 (8.86) years and 28.5 (7.38) years, respectively. The overall mortality risk in patients with CHD was 16.51 times higher (95% CI, 15.29-17.83; $P < .001$) than that in matched controls. According to the hierarchical CHD classification[21] (**Table 1**), the first group of patients with CHD with the most severe complex defects (ie, common arterial trunk, transposition of the great vessels, double inlet ventricle, hypoplastic left heart syndrome, tetralogy of Fallot, and atrioventricular septal defect) had the highest mortality risk at 64.07 (95% CI, 53.39-76.89; $P < .001$) over the entire study period compared with controls. Furthermore, in less complex congenital malformations, such as those found in the second group (ie, septal defects, patent ductus arteriosus, coarctation of the aorta, and Ebstein anomaly), the mortality risk was 10.90 times greater compared with the risk in controls (95% CI, 9.65-12.32; $P < .001$).

Table 2 presents the mortality risk by age and birth period. The overall mortality was higher in patients with CHD than that in controls in all age and birth cohort groups. Survivorship among children younger than 5 years was increased from 96% in those born in 1970-1979 to 98% in those born in 1990-1993. However, the highest mortality risk was found among children younger than 5 years in all birth cohorts. The HRs were 225.84 (95% CI, 136.84-372.70) in patients with CHD who were born in 1970-1979, 136.51 (95% CI, 92.98-200.42) in those born in 1980-1989, and 33.47 (95% CI, 22.54-49.70) in those born in 1990-1993. Therefore, the relative and absolute risks declined with increasing age and by increasing birth decade. However, mortality remained high during adolescence, with HRs of 16.93 (95% CI, 12.18-23.51) in patients with CHD aged 10 to 17 years who were born in 1970-1979, 11.90 (95% CI, 8.63-16.42) in those born in 1980-1989, and 9.16 (95% CI, 6.01-13.96) in those born in 1990-1993.

Figure 1 shows Kaplan-Meier curves for the probability of death in the study population from birth during long-term follow-up. The probability of death in patients with CHD was significantly greater than that in controls (12% vs 2%) until age 42 years. The mortality rate was markedly greater during the first 4 years after birth (Table 2), and it continued to be increased, albeit at a lower rate, during adulthood. eFigure 1 in the Supplement shows survival separately for men and women. Cumulative survival was 87% in men and 90% in women compared with 98% and 99% in controls, respectively.

Curves showing the probability of death in patients with CHD by birth cohort compared with controls are shown in **Figure 2**. Patients with CHD who were born in 1990-1993 had a significantly lower cumulative mortality of 4% at 18 years compared with almost 6% in patients born in 1980-1989 and 8% in those born in 1970-1979.

eFigure 2 in the Supplement shows Kaplan-Meier survival curves for the study population according to the hierarchical CHD classification. The first and fourth CHD groups had the lowest survival rates, at 68% for the first group and 84% for the fourth in those younger than 42 years.

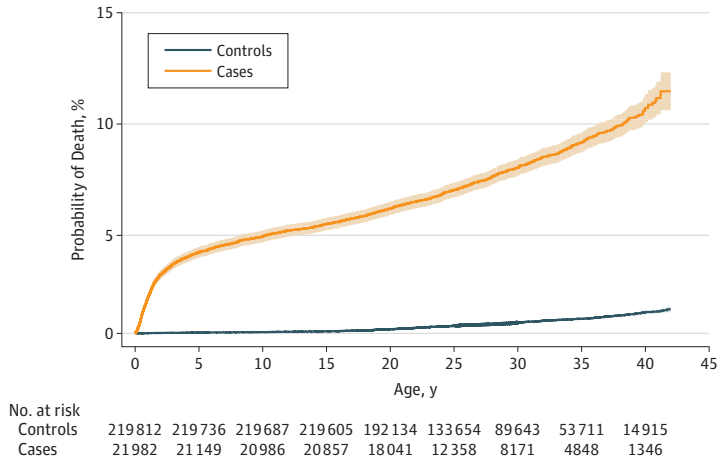
In an additional sensitivity analysis, we studied survivorship during adulthood in all patients with the diagnosis of CHD

Table 2. Mortality Risk in the Study Population by Different Periods of Birth and Age

Age, y	Congenital Heart Disease		Controls		HR for Mortality (95% CI)
	Death Events, No.	Mortality Rate per 100 000 Person-years	Death Events, No.	Mortality Rate per 100 000 Person-years	
Born in 1970-1979					
0-4	353	966.87	16	4.25	225.84 (136.84-372.70)
5-9	77	215.68	17	4.51	47.76 (28.25-80.76)
10-17	92	162.90	58	9.63	16.93 (12.18-23.51)
18-29	179	215.41	217	24.06	8.96 (7.36-10.93)
30-42	139	289.75	233	43.91	6.61 (5.36-8.16)
Born in 1980-1989					
0-4	374	844.36	28	6.14	136.51 (92.98-200.42)
5-9	62	142.20	22	4.82	29.49 (18.13-47.96)
10-17	79	114.14	70	9.60	11.90 (8.63-16.42)
18-29	130	180.94	285	37.16	4.87 (3.96-5.99)
30-42	3	221.06	5	33.99	6.52 (1.56-27.30)
Born in 1990-1993					
0-4	106	404.37	32	12.03	33.47 (22.54-49.70)
5-9	24	92.30	10	3.76	24.52 (11.72-51.26)
10-17	41	99.14	46	10.82	9.16 (6.01-13.96)
18-29	14	138.48	34	32.42	4.27 (2.29-7.95)
30-42	NA	NA	NA	NA	NA

Abbreviations: HR, hazard ratio; NA, not available.

Figure 1. Overall Probability of Death in Patients With Congenital Heart Disease and Controls



The probability of death is shown from birth to 42 years. Shaded areas indicate 95% CIs.

who were alive at 18 years. Survival was still lower in young adults with CHD compared with controls. However, there was no significant difference in survivorship between birth cohorts, with HRs of 7.79 (95% CI, 6.72-8.96) in patients who were born in 1970-1979, 4.91 (95% CI, 3.99-6.02) in those born in 1980-1989, and 4.26 (95% CI, 2.29-7.94) in those born during 1990-1993. **Figure 3** shows the probability of death in patients with CHD older than 18 years with the rate of death almost the same in all birth cohorts.

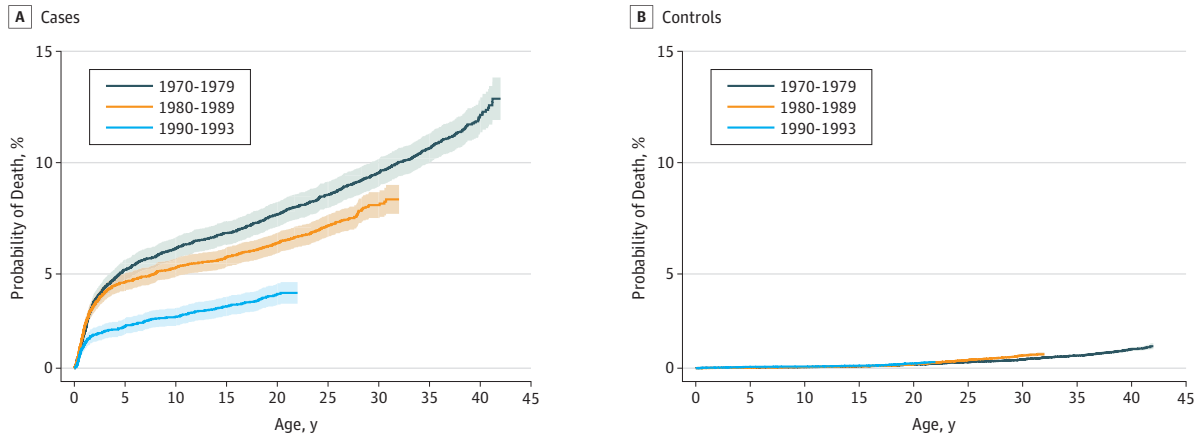
A total of 8352 of 21 982 patients (38.0%) with CHD underwent at least 1 cardiac surgical procedure during 42 years of follow-up. Of these patients, 245 (2.9%) died postoperatively.

Discussion

Analysis of Swedish national, registry-based data showed that the mortality risk was almost 17 times greater in children and young adults with CHD compared with matched controls during a mean follow-up of 27.0 years. However, there was a substantially lower mortality rate in the cohort born in 1990-1993.

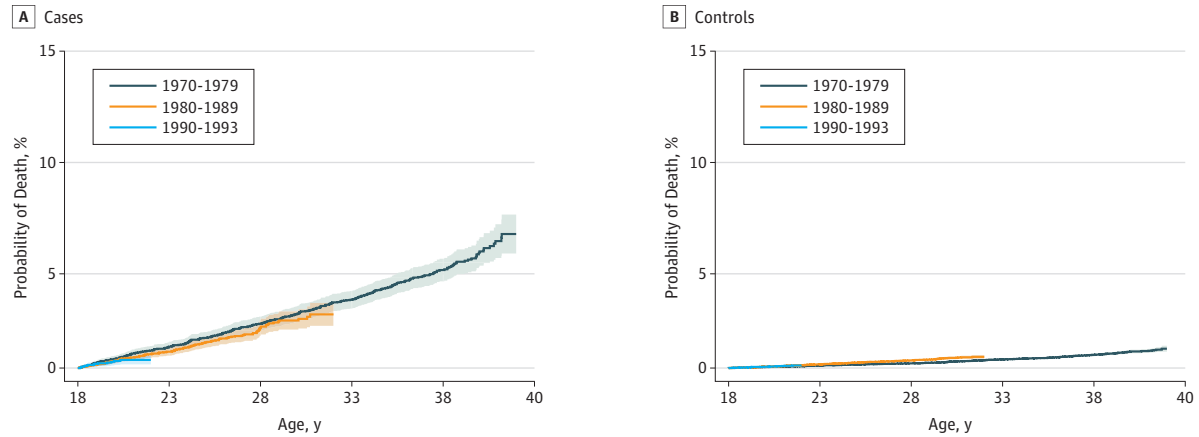
A recent nationwide analysis of perioperative mortality and CHD indicated that, although perioperative mortality in children declined during the 1970s and 1980s, significant improvement was observed in the 1990s and 2000s.[6] The decline in

Figure 2. Probability of Death by Birth Cohort in Patients With Congenital Heart Disease and Controls



The probability of death is shown for cases (A) and controls (B) from birth to 42 years. Shaded areas indicate 95% CIs.

Figure 3. Probability of Death by Birth Cohort in Patients With Congenital Heart Disease During Adulthood



The probability of death is shown for cases (A) and controls (B). Shaded areas indicate 95% CIs.

mortality in Sweden in the 1990s is considered to be the result of improvements in perinatal and pediatric care, early diagnosis of CHD, and centralization of CHD surgeries into 2 cardiothoracic centers in Sweden at the beginning of the 1990s.[26,27] Although the birth incidence of most CHD is relatively constant, improvements in preoperative diagnostics, surgical techniques, intensive care, and anesthesiology have resulted in fewer reoperations and better long-term outcomes.[6] In addition, more recent advances in surgical technique (ie, Norwood surgery for hypoplastic left heart syndrome,[28] staged palliation for children with univentricular hearts,[29] and arterial switch procedure in patients with transposition[30,31]) have been implemented in Sweden, most after 1990. Future studies will show whether even further increases in survivorship will occur in patients born after 1993.

A recent study of a selected CHD population from a single tertiary center showed that young adults with isolated simple defects, such as atrial sepal defect and ventricular septal defect, presented with a mortality rate similar to that of the general population during a median follow-up of 9.1 years.[32] In this previous study, more-complex lesions had a much higher mortality risk, similar to that of our study in the complex-lesion group. However, patients with simple CHD defects are not always followed up systematically by tertiary centers. The findings of mortality in patients with CHD similar to that of the general population in the study by Diller et al were unexpected.[32]

A nationwide registry study from Denmark showed that mortality in patients with less-complex forms of CHD, such as atrial sepal defect, ventricular septal defect, pulmonary stenosis, and patent ductus arteriosus, was almost twice that of controls.[20] The patients of this previous study were born between 1948 and 1973 and received the CHD diagnosis and were entered into a registry between 1963 and 1993. That study focused on mortality in patients older than 15 years. Despite the diagnostic difficulties of identifying simple CHD during the 1950s to 1960s and the different access to treatment at that time, the increased mortality that was observed among patients with uncomplicated CHD is of interest. Using a nationwide registry with a later generation of patients, we also found that the risk of death in patients with less-complex CHD (second to fifth group of CHD lesions) was between 8-fold and 22-fold higher compared with matched controls.

We found the largest decrease in mortality among patients with CHD between birth and 4 years. Similar to our results, the findings of Boneva et al[9] showed that the highest age mortality, as well as the greatest decline in mortality in the United States, occurred in children younger than 5 years between 1979 and 1997.

A Dutch registry study showed that mortality in adults with CHD was increased during 2001-2009, especially in younger patients compared with controls,[19] which is similar to our findings. The risk of death, particularly from congestive heart failure, was increased equally in younger and older patients compared with adjusted controls from the general population. However, this Dutch study included only adults with CHD (median age at inclusion, 32.4 years), it had a shorter follow-up period compared with that of adjusted controls, and it had only 95% follow-up for mortality.

One of the strengths of the present study is that it was based on nationwide data with almost complete follow-up and it represented the entire CHD population in Sweden. Furthermore, the relative hazard of death was estimated from a control study population that was matched by birth year, sex, and county. However, there are also some limitations to our study. First, the present study was based on registers and no other clinical data were available. Second, the outpatient register is available only since 2000. Patients with CHD whose care was managed only in outpatient clinics before that time could not be identified. Third, there was no formal validation of diagnoses. Patients with CHD are generally treated in a few highly specialized centers in Sweden, which should minimize misclassification. For legal reasons, we were required to use only coded data and thus were unable to validate the CHD diagnoses through hospital records. Major cardiovascular diseases have been validated externally and by individual researchers with an overall positive predictive value of diagnosis of 85% to 95% in the register.[33] Therefore, coding bias may have been present in the current national registry study, but not to the extent that it could have greatly affected our results. Finally, the study period spanned 3 different versions of ICD codes, and changes in the codes may have affected the comparability of patients with CHD.

Conclusions

Our study shows that the overall mortality risk in children and young adults with CHD in Sweden is markedly higher compared with that of matched controls. There was a significant reduction in the mortality rate in patients with CHD between 1970 and 1993, predominantly as a result of declining early deaths. However, although the mortality risk has decreased by more than 100 times, children with CHD younger than 5 years and born in the early 1990s still have a mortality risk more than 33 times higher than the risk in children without CHD. Our results indicate the need for research on the mechanisms of death in this group of young patients.

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Study concept and design: Mandalenakis, Rosengren, Skoglund, Lappas, Dellborg.
Acquisition, analysis, or interpretation of data: Mandalenakis, Lappas, Eriksson, Dellborg.
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