International Journal of Cardiology 276 (2019) 81–86

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Depression and anxiety are associated with high health care utilization and mortality among adults with congenital heart disease☆

Michal Benderly [a,b,*], Ofra Kalter-Leibovici [a,b], Dahlia Weitzman [b,c], Leonard Blieden [d], Jonathan Buber [b,e], Alexander Dadashev [d], Efrat Mazor-Dray [f], Avraham Lorber [g], Amiram Nir [h], Sergei Yalonetsky [g], Yaron Razon [f,i], Gabriel Chodick [b,c], Rafael Hirsch [d], for the Israeli Congenital Heart Disease Research Group

[a] Cardiovascular Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Ramat-Gan, Israel
[b] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[c] Morris Kahn & Maccabi Institute for Research and Innovation, Maccabi Healthcare Services, Israel
[d] Adult Congenital Heart Disease Unit, Rabin Medical Center, Sorasky Faculty of Medicine, Tel Aviv University, Petach Tikva, Israel
[e] Leviev Heart Center, Sheba Medical Center, Ramat-Gan, Israel
[f] Ben-Gurion University of the Negev, Negev, Israel
[g] Pediatric Cardiology and GUCH Unit, Rambam Health Care Campus, Technion Faculty of Medicine, Haifa, Israel
[h] Department of Pediatric Cardiology, Hadassah, Hebrew University Medical Center, Jerusalem, Israel
[i] Pediatric cardiology service, Pediatric Department, Assuta Ashdod University Hospital, Ashdod, Israel

ARTICLE INFO

*Article history:*
Received 20 June 2018
Received in revised form 31 July 2018
Accepted 3 September 2018
Available online 12 September 2018

*Keywords:*
Adult congenital heart disease
Depression
Anxiety
Health care utilization
Mortality

ABSTRACT

*Background:* The significance of depression/anxiety among ACHD patients in terms of health care utilization is unknown and data on the association with mortality are scarce.
*Methods:* Analyses comprised 8334 ACHD patients, age ≥ 18 years, insured by a large healthcare organization (2007–2011). Depression/anxiety were determined by diagnoses and treatments recorded in the organization database. Adjusted utilization relative rates (RRs) were estimated with negative binomial models and mortality hazard ratios (HRs) with the Cox proportional hazard model.
*Results:* ACHD patients with depression/anxiety ($N = 2950$, 35%) were more likely to be older (mean ± SD: 54 ± 17 vs. 45 ± 18 years), women (61% vs. 45%), and have comorbidities than counterparts without depression/anxiety. Following multivariable adjustment, patients with depression/anxiety had more primary care and cardiology clinic visits, more emergency department visits and more hospitalizations. RRs (95% confidence interval) were: 1.31 (1.27–1.35); 1.07 (1.01–1.13); 1.60 (1.46–1.77); and 1.18 (1.08–1.29) respectively, for diagnosis before the study period, and 1.36 (1.31–1.42); 1.22 (1.14–1.30); 1.43 (1.24–1.60) and 1.47 (1.33–1.64), respectively, for diagnosis during the study. Stratifying by age, the highest adjusted primary care and cardiology visit RRs were found among 18–24 years old patients and the lowest among patients ≥65 years.
Between 2007 and 2017, 905 patients died. Depression/anxiety were associated with increased mortality risk with adjusted HRs: 1.10 (95% CI: 0.94–1.29) for past diagnosis and 1.40 (1.17–1.67) for study period depression/anxiety diagnosis.
*Conclusions:* Depression/anxiety in ACHD patients is associated with increased health-care utilization and a higher risk of death. The efficacy of addressing patients' psychosocial needs in optimizing health-care utilization and improving prognosis needs further evaluation.



## 1. Introduction

Since the middle of the 20th century, the number of congenital heart disease patients surviving beyond childhood has increased dramatically, thanks to significant advances in diagnosis, interventions and follow-up [1–4]. However, even with early correction of the congenital defect, patients surviving into adulthood remain at risk of repeated cardiac procedures, complications, and premature death [5]. The entailed life-long challenges of coping with illness in addition to neurodevelopmental and behavioral problems related to the congenital disease and therapeutic procedures, place these patients at increased risk of psychiatric and emotional problems [6,7].

Mental distress and disorders are associated with increased health care utilization and cost among the general population [8–10] and

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Cardiovascular Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Ramat-Gan, Israel.
*E-mail address:* bender@post.tau.ac.il (M. Benderly).

https://doi.org/10.1016/j.ijcard.2018.09.005
0167-5273/

among patients with chronic morbidities including diabetes, chronic obstructive pulmonary disease, and heart failure [11–15]. Patients with acquired chronic morbidities and concomitant depression or anxiety (depression/anxiety) have poorer prognosis than counterparts without depression/anxiety [16–18]. It is unclear whether depression/anxiety carry similar risks for adult congenital heart disease (ACHD) patients, who contrary to patients with age-related acquired morbidities, face lifetime consequences of their congenital condition. A recent NHLBI/ACHA working group report identified cognitive and psychological outcomes among ACHD patients as a priority research topic [19]. To date, the significance of depression/anxiety, in terms of health care utilization, among ACHD patients has not been investigated and data on the association with survival are limited [20].

The objective of the current study therefore, was to evaluate the association between depression/anxiety and health care utilization and mortality among a large representative cohort of ACHD patients.

## 2. Methods

### 2.1. Setting and patients

Under a national health insurance act, all Israeli citizens have universal access to primary to tertiary care provided by four competing, nonprofit healthcare organizations. [21]. For the purpose of this observational study, we retrospectively identified ACHD patients through the central computerized database of the second largest healthcare organization in the country (Maccabi Healthcare Services; MHS), covering at the time of the study 25% of the population nationwide, without restriction. Patients were included in the study if they were ≥18 years old (range: 19–97; median: 47), had documentation of at least one congenital heart disease diagnosis or specific repair procedure (see Appendix A), and were insured by MHS during the study period (January 2007–December 2011).

### 2.2. Variable definition

Anonymized data retrieved comprised demographic characteristics, and information on congenital cardiac and non-cardiac anomalies, and acquired morbidities. Health care utilization during the studied period included primary-care and cardiology consultations, visits to an emergency department (ED) not resulting in hospitalization, and hospitalizations.

Depression/Anxiety were determined based on diagnoses documented in the patient's medical record before or during the studied period (International Classification of Diseases, Ninth Revision (ICD-9) codes: 296.2–296.36, 311, 300.0, 300.2, 300.4; $N = 2684$) or purchase of antidepressant drugs (ATC code: N06A, excluding benzodiazepines) at least 3 times/year or covering at least 80% of the study period ($N = 266$).

The congenital heart disease complexity for each patient was categorized based on the 32nd Bethesda Conference Report as: simple, moderate, severe or unclassifiable, according to the most severe congenital heart defect of the patient [3].

Socioeconomic status (SES) was determined by the patient neighborhood characteristics [22] ranging between 1, the lowest rank and 10, the highest rank. Comorbidities were summarized with the Charlson comorbidity index based on chronic and hospital diagnoses [23]. The index is a summary of 17 comorbidity categories, weighted according to severity. Long-term vital status was obtained by MHS from the Israel National Social Insurance Institute through May 2017.

### 2.3. Ethical considerations

The study conforms to the declaration of Helsinki and was approved by MHS and the Sheba Medical Center institutional review boards. No informed consent was required.

### 2.4. Statistical methods

Data were analyzed with SAS Version 9.4 (SAS Institute Inc., Cary, NC). Age adjustment for rates (%) and service utilization per 5 person-years were computed by direct standardization with the entire cohort as the reference. The Cochran-Mantel-Haenszel general association test was used to compare rates while controlling for age.

We examined the association between heart defect type and depression/anxiety following a Bonferroni correction of critical level for $p$ values to account for multiple comparisons.

Negative binomial models with a time logarithm offset were used to study the association between depression/anxiety and health service utilization rate ratios (RRs). The variables considered for entry in the models included: age, sex, SES, number of heart anomalies, missing heart defect type, congenital heart disease complexity, non-cardiac congenital defects, and acquired comorbidities (as time since the diagnosis of each comorbidity, relative to the study period; 100% if diagnosed prior to the study period). Hospitalizations during the study period were also considered in models for clinic visits, and outpatient cardiology follow-up for ED visits and hospitalizations models.

Comparison of survival curves following direct age-adjustment was performed with a marginal log-rank test pooled over age strata. The association between depression/anxiety and mortality through 2017 was estimated with the Cox proportional hazard model. The validity of the proportional hazard assumption was examined by a model including depression/anxiety as a time-dependent explanatory variable. No significant deviation from the proportional hazard assumption was detected. Model calibration was evaluated with the Grønnesby and Borgan goodness of-fit-test, using the method proposed by May and Hosmer [24]. The predictive discrimination ability of each model was evaluated using Harrel's C-statistic [25]. Age and multivariable-adjusted parsimonious models showed good calibration and discrimination with C-statistics above 0.8 for all models. Candidate predictors and possible confounders for the different multivariable models were selected based on their expected association with the relevant endpoint based on previous research, and clinical judgment and univariate age-adjusted associations.

## 3. Results

Among 8334 ACHD patients identified, 2073 (25%) had depression and 1973 (24%) had anxiety recorded in the medical record before or during the study period. Overall, 2950 (35%) had depression/anxiety, of whom 37% had both. Patients with depression/ anxiety were, on average, 8 years older than counterparts without depression/anxiety (Table 1). Following age adjustment, patients with depression/anxiety were more likely to be women, have lower SES and comorbidities such as diabetes, hypertension, hyperlipidemia and, stroke or transient ischemic attack (TIA) (Table 1).

Atrial septal defect (ASD; 21%) was the most common malformation followed by aortic valve stenosis or insufficiency (20%). ASD, anomalies of the aorta, and mitral valve stenosis or insufficiency were significantly more prevalent among patients with depression/anxiety (Table 2). ACHD patients with depression/anxiety were slightly more likely to have a non-complex disease. The distribution of or the number of heart defects was not significantly different between the groups once age was accounted for.

**Table 1**
Characteristics of 8334 adult congenital heart disease patients by depression/anxiety.

| | Depression/anxiety | | | | $p$ |
|---|---|---|---|---|---|
| | No | | Yes | | |
| *N* | 5384 | | 2950 | | |
| Age mean ± SD | 45.2 ± 17.7 | | 54.1 ± 17.4 | | <0.0001 |
| Women *N* (%) | 2438 (44.7) | | 1794 (60.8) | | <0.0001 |
| SES score *N* (%) | | | | | |
| 9–10 | 814 | (15.6) | 405 | (13.6) | 0.02 |
| 7–8 | 1756 | (32.6) | 926 | (32.2) | |
| 5–6 | 2025 | (38.0) | 1132 | (38.6) | |
| 3–4 | 657 | (12.3) | 414 | (14.2) | |
| 1–2 | 87 | (1.5) | 37 | (1.4) | |
| Comorbidities and complications *N* (%) | | | | | |
| Cancer | 408 | (8.6) | 356 | (10.1) | 0.03 |
| Chronic kidney disease | 691 | (15.0) | 616 | (16.4) | 0.05 |
| Diabetes mellitus | 600 | (12.7) | 527 | (14.7) | 0.006 |
| Hypertension | 1898 | (39.6) | 1528 | (43.8) | <0.0001 |
| Hyperlipidemia | 2214 | (44.8) | 1638 | (48.9) | <0.0001 |
| Ischemic heart disease | 953 | (20.3) | 772 | (21.3) | 0.2 |
| Heart failure | 424 | (9.1) | 398 | (10.9) | 0.003 |
| Stroke/TIA | 347 | (7.1) | 369 | (10.7) | <0.0001 |
| Arrhythmia | 1065 | (21.8) | 861 | (25.6) | <0.0001 |
| Pulmonary arterial hypertension | 49 | (1.0) | 42 | (1.2) | 0.4 |
| Charlson comorbidity index *N* (%) | | | | | |
| 0 | 1491 | (27.7) | 232 | (12.5) | <0.0001 |
| 1–2 | 1541 | (28.6) | 384 | (20.6) | |
| 3–4 | 901 | (16.7) | 374 | (20.1) | |
| 5+ | 1451 | (27.0) | 870 | (46.8) | |
| Non cardiac congenital anomaly[a] *N* (%) | | | | | |
| 0 | 4893 | (90.6) | 2608 | (89.1) | 0.07 |
| 1 | 452 | (8.7) | 310 | (9.9) | |
| 2+ | 39 | (0.7) | 32 | (1.0) | |

Percent are age adjusted except for age.
HD - heart disease; IQR-interquartile range; OR-age adjusted odds ratio of depression/Anxiety. Ref-Reference value is men for women, or without the characteristic if not otherwise specified; SES- Socioeconomic status (ranging between 1 (lowest SES) and 10 (the highest SES), missing for 81 patients; TIA-transient ischemic attack.
[a] Number of body systems affected.

**Table 2**
Congenital heart defects among 8334 adult congenital heart disease patients according to depression/anxiety.

| | Depression/anxiety | | | | p |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | N | (%) | N | (%) | |
| Heart defect type | | | | | |
| Atrial septal defect | 1012 | (19.1) | 707 | (23.5) | <0.0001* |
| Aortic valve stenosis/insufficiency | 1132 | (20.7) | 515 | (18.3) | 0.004 |
| Anomalies of the aorta | 258 | (4.8) | 200 | (6.4) | 0.0006* |
| Ventricular septal defect | 670 | (11.4) | 261 | (10.9) | 0.4 |
| Mitral valve stenosis/insufficiency | 402 | (7.8) | 316 | (10.1) | 0.0004* |
| Pulmonary valve anomaly | 293 | (5.0) | 95 | (3.6) | 0.02 |
| Endocardial cushion | 281 | (5.1) | 157 | (5.9) | 0.2 |
| Tetralogy of fallot | 130 | (2.2) | 34 | (1.4) | 0.02 |
| Common or single ventricle | 103 | (1.9) | 52 | (1.8) | 0.5 |
| Ebstein anomaly of tricuspid valve | 72 | (1.2) | 30 | (1.1) | 0.7 |
| Transposition of great arteries | 27 | (0.4) | 11 | (0.5) | 0.7 |
| Other defects | 1828 | (34.7) | 947 | (31.3) | 0.001* |
| Defect type not specified | 314 | (6.0) | 193 | (5.8) | 0.98 |
| Number of heart defects | | | | | |
| 1 | 4498 | (84.2) | 2501 | (83.7) | 0.7 |
| 2 | 674 | (12.0) | 345 | (12.4) | |
| 3+ | 212 | (3.8) | 104 | (3.9) | |
| Congenital heart disease complexity | | | | | |
| Simple | 2710 | (50.0) | 1554 | (53.8) | 0.0001* |
| Intermediate | 1172 | (20.9) | 613 | (22.0) | |
| Complex | 231 | (4.1) | 93 | (3.4) | |
| Unclassifiable | 1271 | (25.0) | 690 | (20.9) | |

Percent presented are age adjusted. A patient can have more than one defect.
Congenital heart disease complexity categorized based on the 32nd Bethesda Conference [3].
* Significant under a Bonferroni correction for multiple comparisons of heart defect types ($p < 0.0038$).

Thirty-seven percent of patients with depression/anxiety purchased an anxiolytic or antidepressant drug during the study period, and 39% of treated patients received selective serotonin reuptake inhibitors (SSRI; Supplemental Table S-3). Among patients with depression/anxiety, those purchasing antidepressant or anxiolytic medications were older than patients who did not [median (interquartile range): 57 (44–71) vs. 51 (36–64) years, respectively; $p < 0.0001$]. Patients with depression/anxiety who purchased anti depression/anxiety medication, had higher age-adjusted prevalence of arrhythmias (32%) and ischemic heart disease (29%) compared to patients who did not purchase any depression/anxiety drug during the studied period (28%; $p = 0.026$ and 24%; $p = 0.0005$, respectively). No other significant difference was found between treated and untreated patients (data not presented).

### 3.1. Depression/anxiety and health service utilization

We examined health service utilization separately in patients with a past documentation of depression/anxiety ($N = 1860$) and in those with a more recent diagnosis recorded during the studied period ($N = 1090$), compared to patients with no depression/anxiety ($N = 5384$). As depicted in Table 3, almost all ACHD patients visited a primary care physician at least once during the 5 year study period (2007–2011). The age-adjusted number of primary care visits was higher among patients with depression/anxiety than for patients without, regardless of the time of diagnosis (47 vs 33 visits /5 person-years). Patients with depression/anxiety were also more likely to visit a cardiologist (87% and 83% among recent or past diagnosis respectively, compared to 80% among patients with no depression/anxiety; $p < 0.0001$) and had, on average, more consultations per 5 person-years (Table 3). Similar associations were found for men and women, when examined separately (Supplemental Table S-1).

Depression/anxiety was accompanied by higher utilization of inpatient services as well. Patients with depression/anxiety were more likely to visit an ED or to be hospitalized, with the highest prevalence among those with depression/anxiety diagnosis during the study period. The age-adjusted number of hospitalizations and in-hospital days ranged between 5.2/5 person-years for patients with no depression/anxiety to 10.4 for patients with a recent diagnosis (Table 3).

Following multivariable adjustment, patients with a past depression/anxiety diagnosis had 31% more primary care visits, 7% more cardiology consultations, 60% more visits to ED, and 18% more hospitalizations than patients without depression/anxiety. The rates were even higher for patients who were diagnosed with anxiety/depression for the first time during the study period (Table 3). Estimates from models with depression/anxiety as a binary variable (regardless of time of diagnosis) are in line with the results presented in Table 3 (Supplemental Table S-4).

The associations between depression/anxiety and doctor visits were modified by age in a dose-response manner (Supplemental Fig. S-2). While, as expected, older patients visited more often, the highest adjusted RRs for both primary care ($p < 0.0001$) and cardiology ($p = 0.0046$) visits were found among young ACHD patients (age 18–24) and the lowest among patients older than 64 years. The interaction between age and depression/anxiety for ED visits was also significant ($p < 0.0001$) with less consistent direction. There was no significant

**Table 3**
Age adjusted health care utilization among adult congenital heart disease patients during the study period according to time of depression/anxiety diagnosis.

| | Depression/anxiety diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | No | | Diagnosed in the past | | Diagnosed during the study period | |
| N | 5384 | | 1860 | | 1090 | |
| Visited at least once[d] N (%[e]) | | | | | | |
| Primary care | 5312 | (98.7) | 1842 | (99.1) | 1089 | (99.9) |
| Outpatient cardiology | 4246 | (80.3) | 1574 | (83.1) | 956 | (87.0) |
| ED visits | 2403 | (47.2) | 1077 | (52.6) | 636 | (55.5) |
| Hospitalizations | 2108 | (41.5) | 976 | (47.5) | 580 | (50.4) |
| Healthcare encounters/5 years[f] (95% CI) | | | | | | |
| Primary care | 33.5 | (33.3–33.8) | 47.4 | (46.8–48.0) | 46.9 | (46.2–47.7) |
| Outpatient cardiology | 4.9 | (4.8–5.0) | 5.3 | (5.1–5.5) | 6.0 | (5.7–6.2) |
| ED visits | 0.7 | (0.7–0.8) | 1.3 | (1.2–1.4) | 1.1 | (1.0–1.3) |
| Hospitalizations | 1.0 | (0.9–1.0) | 1.3 | (1.2–1.4) | 1.7 | (1.5–1.8) |
| Hospital days | 5.2 | (5.1–5.3) | 7.0 | (6.8–7.2) | 10.4 | (10.1–10.7) |
| Age adjusted RR (95% CI) | | | | | | |
| Primary care | Ref | | 1.43 | (1.37–1.48) | 1.44 | (1.38–1.51) |
| Outpatient cardiology | Ref | | 1.10 | (1.04–1.17) | 1.24 | (1.15–1.33) |
| ED visits | Ref | | 1.78 | (1.61–1.95) | 1.52 | (1.35–1.71) |
| Hospitalizations | Ref | | 1.36 | (1.24–1.50) | 1.66 | (1.48–1.86) |
| Multivariable adjusted RR (95% CI) | | | | | | |
| Primary care[a,b] | Ref | | 1.31 | (1.27–1.35) | 1.36 | (1.31–1.42) |
| Outpatient cardiology[d] | Ref | | 1.07 | (1.01–1.13) | 1.22 | (1.14–1.30) |
| ED visits[a,c] | Ref | | 1.60 | (1.46–1.77) | 1.43 | (1.24–1.60) |
| Hospitalizations[c] | Ref | | 1.18 | (1.08–1.29) | 1.47 | (1.33–1.64) |

CI-Confidence interval, ED- emergency department visits without hospitalization, IQR-interquartile range, RR- Rate ratio, Ref-Reference value.
[d] At least one encounter in the data collection period (2007–2011); [e] Adjusted for age; [f] Age adjusted number of encounters per 5 patient years.
All parsimonious multivariable models included: Sex, age, congenital heart disease complexity, number of congenital cardiac defects, comorbidities (cancer/dialysis, diabetes mellitus, hypertension, cardiovascular disease, heart failure, arrhythmia: included as time since diagnosis of each comorbidity relative to the study period- see Methods), and socioeconomic status.
Additional variables included:
[a] Other congenital defects.
[b] Hospitalization during the study period.
[c] Followed by a cardiologist.

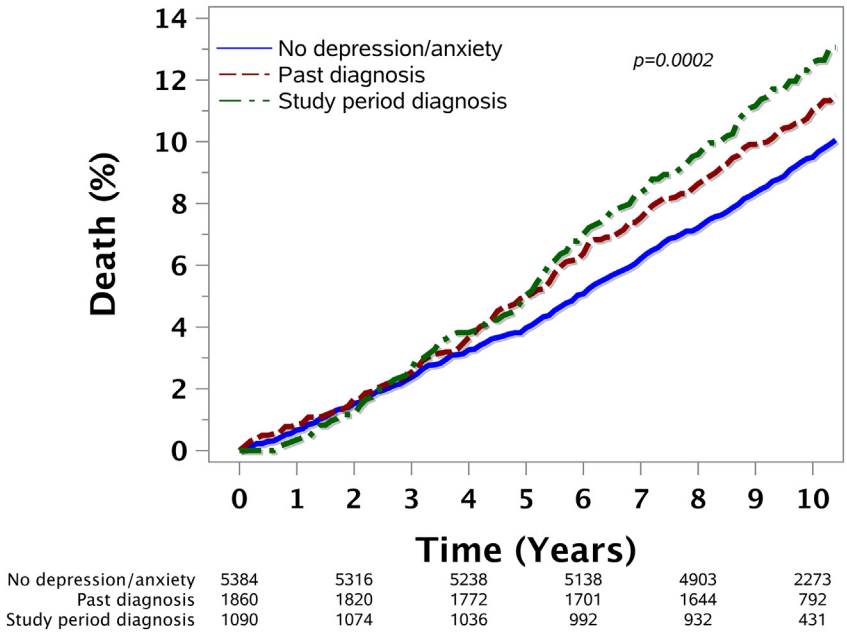


**Fig. 1.** Age adjusted cumulative mortality probability by depression/anxiety.

interaction between anxiety/depression and age for hospitalization rate (Supplemental Fig. S-2).

When added to the model, antidepressants were significantly associated with hospitalizations (RR: 1.16, 95% CI: 1.02–2.32) but not with utilization of other health services. Anxiolytics, on the other hand, were associated with increased utilization of both outpatient and inpatient services (RR: 1.15 for primary care visits, 1.20 for ED visits and hospitalizations and 1.25 for cardiology outpatient consultations; $p < 0.001$ for all comparisons). In all models, adding drugs purchased only slightly attenuated the association between depression/anxiety and health care unitization. Examined separately, SSRIs were associated with increased health care utilization, with a RR of 1.17 (95% CI: 1.10–1.24) for primary care visits, 1.17 (95% CI: 1.06–1.29) for cardiology outpatient visits, 1.23 (95% CI: 1.04–1.45) for ED visits, and 1.21 (95% CI: 1.18–1.24) for hospitalizations. The results of sensitivity analyses examining depression and anxiety separately were in-line with the results of the multivariable models described above (Supplemental Table S-2).

### *3.2. Depression/anxiety and mortality*

Over a median period of 10 years (80,985 person-years in total) 905 patients (11%) died. Adjusting for age, depression/anxiety was associated with increased long-term mortality risk (Fig. 1) particularly among men (Supplemental Fig. S-1). The age-adjusted mortality rates/1000 person-years were 10 for patients without depression/anxiety (reference group), 12 for patients with a past diagnosis (age adjusted HR: 1.18, 95% CI: 1.01–1.37) and 14 for patients with depression/anxiety diagnosed during the study period (HR: 1.43, 95% CI: 1.20–1.70). The corresponding HRs following adjustment for age, SES, missing specific diagnosis, congenital heart disease complexity, and comorbidities (Charlson index) were: 1.10 (95% CI: 0.94–1.29) for past diagnosis and 1.40 (95% CI: 1.17–1.67) for a recent diagnosis of depression/anxiety. The results were similar when each comorbidity was included in the model separately (HR for past diagnosis: 1.09, 95% CI: 0.93–1.28; and for diagnosis during the study period: 1.41, 95% CI: 1.18–1.69). Depression/anxiety treatment added to the model was not associated with mortality, nor was the interaction between depression/anxiety and age or sex.

## 4. Discussion

The current study provides, for the first time, evidence of increased health care utilization among unselected ACHD patients with depression/anxiety. In the largest study so far, we found depression/anxiety documentation in medical records of more than a third of ACHD patients. Depression/anxiety were associated with an increase of both outpatient and inpatient services including primary care and cardiology clinic visits, ED visits and hospitalizations. Furthermore, ACHD patients with depression/anxiety had higher mortality rates, particularly when diagnosed more recently.

The association between depression/anxiety and increased health care utilization is multidirectional. Actual as well as self-imposed physical limitation may increase the risk of metabolic risk factors among ACHD patients. Chronic stress was also reported to be associated with visceral obesity, type 2 diabetes, metabolic syndrome and atherosclerotic disease [26] all leading to increased healthcare needs with advancing age and subsequently to poorer prognosis. Additionally, anxious or depressed patients may overexpress medical symptoms and be less adherent to treatment or health behavior recommendations [9].

Depression/anxiety related relative care utilization rates, in our study, were age dependent. While, as expected, utilization of all services increased with age, younger patients had higher doctor visit rates relative to their age group peers without depression/anxiety. While younger patients seem to be more affected by depression/anxiety, our findings may also reflect the higher prevalence of complex and intermediate congenital disease among them. Conversely, the association between depression/anxiety and health care utilization among older patients, may be attenuated by a higher prevalence of age-related comorbidities or the result of a less severe disease allowing them to survive longer.

<40% of patients with depression/anxiety received pharmacotherapy. The use of certain antidepressants was reported to carry a risk of arrhythmias, venous thromboembolism and sudden cardiac death through QT segment prolongation [27–29]. Diller et al. reported worse prognosis among ACHD patients with depression based on use of antidepressant drugs [20]. It is unclear whether the association is attributed to the depression or to treatment side effects. As observational studies preclude linking the risk of arrhythmias to the treatment received, clinical trials are needed to determine the efficacy and safety of different drug treatments for ACHD patients. No such trials were published to date. Without robust data to support the safety these drugs among ACHD, concerns of

arrhythmia, may have limited the use of antidepressants in certain patients. We did not have information on non-pharmacological interventions, including psychotherapy or other support and therefore could not determine how many patients remained untreated. The grave implication of depression/anxiety among ACHD patients in terms of quality of life, health care utilization, and prognosis, emphasizes the need for adequate psychosocial support for these patients.

Albeit the remarkable improvement in life expectancy over the last decades, ACHD patients remain at increased mortality risk compared to the general population [30,31]. Our findings suggest that depression/anxiety is associated with additional mortality risk despite higher health care utilization. Very few studies have assessed the possible impact of depression/anxiety on prognosis in ACHD patients [20,32]. While we did not find an effect modification by sex, Diller et al. reported lower survival among men using anti depression/anxiety medications and not among women [20].

Nonadherence to treatment is one of the mechanisms by which depression/anxiety may be associated with poor prognosis among ACHD patients [9,20]. Adherence to outpatient clinic appointments in a specialized ACHD center was reported to be associated with improved survival [33].

The fact that the association with mortality was stronger for more recently diagnosed depression/anxiety than for long-standing disease may stem from reverse causality, where depression/anxiety reflect poor health rather than cause it. Although the associations were only slightly attenuated following adjustment for known determinants of each outcome (e.g. age, congenital malformation complexity and comorbidities), residual confounding cannot be ruled out. Nonetheless, as depressive symptoms were linked to short, medium and long-term mortality risk in a meta-analysis of studies of coronary heart disease patients [34], mood disorder may have a direct link to disease progression in these patients.

A number of additional limitations merit attention. Our analysis is based on a single healthcare provider. While the range of healthcare services provided is similar for all providers, some differences may still exist between health plans. Interpretation of our results in other settings with variable access to healthcare services, should take into account service cost and availability, which might differentially affect patients with or without depression/anxiety.

In a study based on administrative and clinical database, diagnosis misclassification should also be considered.

Lack of information on functional limitation did not allow us to assess its role in the association between depression/anxiety and prognosis during the studied period.

We could not determine which patients were under specialized ACHD care. Current guidelines recommend regular follow-up in specialized centers for all ACHD patients at intervals determined by disease complexity [2,35]. Multidisciplinary care offered in ACHD clinics may reduce depression/anxiety risk and improve prognosis among patients, yet only a small fraction of ACHD patients receive such care [36].

## 5. Conclusion

The present study provides important evidence of the higher healthcare burden associated with depression/anxiety among ambulatory ACHD patients. Increased health care utilization among patients with depression/anxiety is particularly evident among younger patients, despite lower depression/anxiety rates. Depression/anxiety was also associated with increased mortality risk among ACHD patients.

In addition to adequate management of the congenital disease as well as acquired comorbidities, addressing patient psychosocial needs is an important part of adequate patients' care. Further research is needed to determine the efficacy of depression/anxiety management in saving unnecessary utilizations and ultimately improving prognosis of ACHD patients.

## Funding

This work was supported by an unrestricted grant from the Maccabi Institute for Health Services Research, Tel-Aviv, Israel.

## Conflict of interest

None declared.

## Acknowledgment

The authors would like to gratefully acknowledge Esma Hertzel for her skillful assistance and support of data retrieval.

## Appendix A

List of congenital heart disease diagnosis and procedure codes:

| Diagnosis | ICD-9 code |
|---|---|
| Congenital cardiovascular disorders of mother | 648.5 |
| Bulbus cordis anomalies and anomalies of cardiac septal closure | 745.0 |
| Transposition of the great arteries | 745.1 |
| Tetralogy of Fallot | 745.2 |
| Double inlet ventricle | 745.3 |
| Ventricular septal defect | 745.4 |
| Atrial septal defect | 745.5 |
| Endocardial cushion defects | 745.6 |
| Cor biloculare | 745.7 |
| defect of septal closure OT | 745.8 |
| Unspecified defects of septal closure | 745.9 |
| Other congenital anomalies of heart | 746.0 |
| Tricuspid atresia and stenosis, congenital | 746.1 |
| Ebstein's anomaly | 746.2 |
| Congenital stenosis of aortic valve | 746.3 |
| Congenital insufficiency of aortic valve | 746.4 |
| Congenital mitral stenosis | 746.5 |
| Congenital mitral insufficiency | 746.6 |
| Hypoplastic left-heart syndrome | 746.7 |
| Other unspecified anomalies of the heart | 746.8, 746.9 |
| Patent ductus arteriosus | 747.0 |
| Coarctation of the aorta | 747.1 |
| Other unspecified anomalies of the aorta | 747.2 |
| Anomalies of the pulmonary artery | 747.3 |
| Anomalies of the great veins | 747.4 |
| Other unspecified anomalies of the circulation | 747.9 |

| Procedure | ICD-9 |
|---|---|
| Production of septal defect in heart | 35.4 |
| Repair of unspecified septal defect of heart with prosthesis | 35.50 |
| Repair of atrial septal defect with prosthesis, open technique | 35.51 |
| Repair of atrial septal defect with prosthesis, closed technique | 35.52 |
| Repair of ventricular septal defect with prosthesis, open technique | 35.53 |
| Repair of endocardial cushion defect with prosthesis | 35.54 |
| Repair of unspecified septal defect of heart with tissue graft | 35.60 |
| Repair of atrial septal defect with tissue graft | 35.61 |
| Repair of ventricular septal defect with tissue graft | 35.62 |
| Repair of endocardial cushion defect with tissue graft | 35.63 |
| Other and unspecified repair of unspecified septal defect of heart | 35.70 |
| Other and unspecified repair of atrial septal defect | 35.71 |
| Other and unspecified repair of ventricular septal defect | 35.72 |
| Other and unspecified repair of endocardial cushion defect | 35.73 |
| Total repair of tetralogy of Fallot | 35.81 |
| Total repair of total anomalous pulmonary venous connection | 35.82 |
| Total repair of truncus arteriosus | 35.83 |
| Total correction of transposition of great vessels, not elsewhere classified | 35.84 |
| Interatrial transposition of venous return | 35.91 |
| Creation of conduit between right ventricle and pulmonary artery | 35.92 |
| Creation of conduit between left ventricle and aorta | 35.93 |

## Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.005.

## References


[1] A.J. Marelli, A. Mackie, R. Ionescu-Ittu, E. Rahme, L. Pilote, Congenital heart disease in the general population: changing prevalence and age distribution, Circulation 115 (2007) 163–172.

[2] H. Baumgartner, P. Bonhoeffer, N.M. De Groot, et al., Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG), ESC guidelines for the management of grown-up congenital heart disease (new version 2010), Eur. Heart J. 31 (2010) 2915–2957.

[3] C.A. Warnes, R. Liberthson, G.K. Danielson, et al., Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (2001) 1170–1175.

[4] G. Webb, B.J. Mulder, J. Aboulhosn, et al., The care of adults with congenital heart disease across the globe: current assessment and future perspective: a position statement from the International Society for Adult Congenital Heart Disease (ISACHD), Int. J. Cardiol. 195 (2015) 326–333.

[5] C.L. Verheugt, C.S. Uiterwaal, D.E. Grobbee, B.J. Mulder, Long-term prognosis of congenital heart defects: a systematic review, Int. J. Cardiol. 131 (2008) 25–32.

[6] L.B. Pauliks, Depression in adults with congenital heart disease-public health challenge in rapidly expanding new patient population, World J. Cardiol. 5 (2013) 186–195.

[7] B.S. Marino, P.H. Lipkin, J.W. Newburger, et al., American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council, Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association, Circulation 126 (2012) 1143–1172.

[8] G. Simon, J. Ormel, M. VonKorff, W. Barlow, Health care costs associated with depressive and anxiety disorders in primary care, Am. J. Psychiatry 152 (1995) 352–357.

[9] J.M. Donohue, H.A. Pincus, Effects of pharmaceutical promotion on adherence to the treatment guidelines for depression, PharmacoEconomics 25 (2007) 7–24.

[10] P.J. Salsberry, E. Chipps, C. Kennedy, Use of general medical services among Medicaid patients with severe and persistent mental illness, Psychiatr. Serv. 56 (2005) 458–462.

[11] L.E. Egede, Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability, Gen. Hosp. Psychiatry 29 (2007) 409–416.

[12] E. Atlantis, R.D. Goldney, K.A. Eckert, A.W. Taylor, P. Phillips, Trends in health-related quality of life and health service use associated with comorbid diabetes and major depression in South Australia, 1998–2008, Soc. Psychiatry Psychiatr. Epidemiol. 47 (2012) 871–877.

[13] E.P. Vamos, I. Mucsi, A. Keszei, M.S. Kopp, M. Novak, Comorbid depression is associated with increased healthcare utilization and lost productivity in persons with diabetes: a large nationally representative Hungarian population survey, Psychosom. Med. 7 (2009) 501–507.

[14] A.M. Chamberlain, K.S. Vickers, R.C. Colligan, S.A. Weston, T.A. Rummans, V.L. Roger, Associations of preexisting depression and anxiety with hospitalization in patients with cardiovascular disease, Mayo Clin. Proc. 86 (2011) 1056–1062.

[15] A.M. Yohannes, T.G. Willgoss, R.C. Baldwin, M.J. Connolly, Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles, Int. J. Geriatr. Psychiatry 25 (2010) 1209–1221.

[16] I. Sokoreli, S.C. Pauws, E.W. Steyerberg, et al., Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study, Eur. J. Heart Fail. 4 (2018 Jan) (Epub ahead of print).

[17] M. Panagioti, C. Scott, A. Blakemore, P.A. Coventry, Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease, Int. J. Chron. Obstruct. Pulmon. Dis. 9 (2014) 1289–1306.

[18] J.J. Man, The medical management of depression, N. Engl. J. Med. 353 (2005) 1819–1834.

[19] M. Gurvitz, K.M. Burns, R. Brindis, et al., Emerging research directions in adult congenital heart disease: a report from an NHLBI/ACHA working group, J. Am. Coll. Cardiol. 67 (2016) 1956–1964.

[20] G.P. Diller, A. Bräutigam, A. Kempny, et al., Depression requiring anti-depressant drug therapy in adult congenital heart disease: prevalence, risk factors, and prognostic value, Eur. Heart J. 37 (2016) 771–782.

[21] B. Rosen, H. Samuel, Israel Health System Review. Health Systems in Transition, 11, Copenhagen European Observatory for Health Care Systems and Policies, 2009 1–226.

[22] Central Bureau of Statistics, Characterization and Classification of Geographical Units by the Socio-Economic Level of the Population, 2013 (S.P. 1694).

[23] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.

[24] S. May, D.W. Hosmer, A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model, Lifetime Data Anal. 4 (1998) 109–120.

[25] F.E. Harrell, K.L. Lee, D.B. Mark, Tutorial in biostatistics: multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors, Stat. Med. 15 (1996) 361–387.

[26] I. Kyrou, C. Tsigos, Stress mechanisms and metabolic complications, Horm. Metab. Res. 39 (2007) 430–438.

[27] P. Pacher, V. Kecskemeti, Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? Curr. Pharm. Des. 10 (2004) 2463–2475.

[28] H. Yekehtaz, M. Farokhnia, S. Akhondzadeh, Cardiovascular considerations in antidepressant therapy: an evidence-based review, J. Tehran Heart Cent. 8 (2013) 169–176.

[29] S.K. Kunutsor, S. Seidu, K. Khunti, Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence, Ann. Med. 12 (2018) 1–17.

[30] G.P. Diller, A. Kempny, R. Alonso-Gonzalez, et al., Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre, Circulation 132 (2015) 2118–2125.

[31] C.L. Verheugt, C.S. Uiterwaal, E.T. van der Velde, et al., Mortality in adult congenital heart disease, Eur. Heart J. 31 (2010) 1220–1229.

[32] P. Kourkoveli, S. Rammos, J. Parissis, A. Maillis, D. Kremastinos, I. Paraskevaidis, Depressive symptoms in patients with congenital heart disease: incidence and prognostic value of self-rating depression scales, Congenit. Heart Dis. 10 (2015) 240–247.

[33] A. Kempny, G.P. Diller, K. Dimopoulos, et al., Determinants of outpatient clinic attendance amongst adults with congenital heart disease and outcome, Int. J. Cardiol. 203 (2016) 245–250.

[34] J. Barth, M. Schumacher, C. Herrmann-Lingen, Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis, Psychosom. Med. 66 (2004) 802–813.

[35] A.B. Bhatt, E. Foster, K. Kuehl, et al., American Heart Association Council on Clinical Cardiology, Congenital heart disease in the older adult: a scientific statement from the American Heart Association, Circulation 131 (2015) 1884–1931.

[36] A.J. Marelli, M. Gurvitz, From numbers to guidelines, Prog. Cardiovasc. Dis. 53 (2011) 239–246.