Long-term Healthcare Utilization, Medical Cost, And Societal Cost In Adult Congenital Heart Disease

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Abstract

Objective**.** Cost-of-illness studies in Adult Congenital Heart Disease (ACHD) have mainly been limited to hospitalizations. This is the first paper to provide a comprehensive overview of inpatient, outpatient, absenteeism- and unemployment-related societal costs. Methods**.** A retrospective longitudinal (2006-2015) database analysis was performed in Belgium combining administrative and clinical databases (n = 10,572). Trends in resource use and costs per patient year were standardized to assess the impact of changes in the patient population composition. Generalized Linear Mixed Models assessed the impact of age, sex, lesion complexity, and time. Costs were converted to 2018 values. Results**.** Medical costs per patient year increased from €3,490 to €4,536 with a milder increase in patients with severe lesions. Although unemployment-related costs decreased, total societal costs increased due to more long-term (≥1yr) invalidity. An increase in long-term invalidity was particularly found in patients ≥30yrs and in patients with mild or moderate lesions. Resource use (e.g., dental care, nursing care, physiotherapy, emergency department) increased substantially in all patient groups over time. The annual percentage of patients with severe lesions receiving any cardiac and specialized cardiac follow-up increased with respectively 11 and 13 percent points to 81% and 52%, with a simultaneous decrease in hospitalization rate. Conclusion**.** Medical cost increases in ACHD are most pronounced in patients with mild and moderate lesions, relatable to their higher age. Economic data are necessary to allocate resources efficiently to ensure sustainable, qualitative care in an ageing patient population with strong increases in medical and long-term invalidity-related costs.

Keywords

Healthcare economics, adult congenital heart disease, health services

1. Introduction

Medical progress in combination with stronger organizational structures and general healthcare improvements have led to a rapidly expanding patient population of adults with congenital heart disease (CHD).[1, 2] Substantial yearly increases in absolute hospitalization numbers have been reported worldwide[3], and have imposed a growing burden on available financial resources.[4]

Cost estimates have mainly been calculated based on hospitalizations and not on outpatient care. Yet, the latter is a key element in adult congenital heart disease (ACHD) care since lifelong follow-up is recommended to timely detect deterioration.[5] According to a recent systematic review, the number of outpatient cardiology visits increased with 8.2-11.4% per year in the past decades.[3] To the best of our knowledge, no cost data have been published on outpatient cardiac care although such data could be beneficial to determine the most appropriate care level.[5] Moreover, literature on other outpatient healthcare utilization (HCU) remains scarce.[6, 7] Previous research on hospitalization and outpatient care showed the importance of stratifying results for age, sex, and lesion complexity.[3]

Furthermore, whether absenteeism and unemployment rates is higher in the ACHD population compared to the general population appeared to differ over countries.[8] Societal cost estimates are scarce.[9]

Hence, a Belgian study was carried out (i) to describe long-term (2006-2015) inpatient and outpatient HCU, (ii) to calculate the related medical costs for the health insurance and the patient ('health expenditures'), as well as the absenteeism- and unemployment-related societal cost, and (iii) to determine the impact of age, sex, time, and lesion complexity.

2. Methods

2.1. Databases

A detailed description of the Belgian Congenital Heart Disease Database combining Administrative and Clinical data (BELCODAC) will be published elsewhere.[10] Briefly, the BELCODAC comprises healthcare utilization data from ten consecutive years (i.e. 2006-2015), and clinical data from the same time period and before (e.g. information about early interventions). Particularly, ten databases from five organizations were merged:

- The Intermutualistic Agency (IMA) is the umbrella organization of the seven Belgian sickness funds. The IMA delivered three population-level databases: (i) the population database (socio-demographic information), (ii) the pharmanet database (medication supply information about medicines), and (iii) the medical claims database (medical care information).

- Statistics Belgium collects, processes and distributes data about the Belgian society, and they delivered four population-level databases: (i) the death certificate database, (ii) the socio-demographic database, (iii) the socio-economic database, and (iv) the IPCAL database (income information).

- Ghent University Hospital, University Hospitals Leuven and St-Luc University Hospitals each provided part of the study population and delivered clinical information.

2.2. Study population

ACHD care is quite well-established in Belgium (11.4M inhabitants) with four specialized hospitals designated to provide the full spectrum of CHD care including congenital cardiac surgery,[11] and established outpatient clinics in affiliated satellite centers. Three out of the four specialized hospitals took part in this study. Ghent University Hospital and University Hospitals Leuven selected all CHD patients who attended the specialized clinic at least once throughout their life. Patients with severe lesions of St-Luc University Hospital were included to ensure a reasonable sample size so that cost-of-illness estimates would be stable for all subgroups.[12] An open cohort study was applied with the inclusion of all patients alive, and 18 years or older on January 1st during at least one year in the study period (2006-2015).

2.3. Outcome measures

Results are reported as the annual percentage of patients requiring a certain type of HCU, and the per patient year number of visits per HCU type. Outpatient cardiology visits were classified into pediatric, ACHD, and general cardiology visits. Other HCU were hospitalizations (both cardiac and non-cardiac) and length of stay (LOS), general practitioner (GP) visits, emergency department (ED) visits, outpatient visits to non-cardiac medical specialists, dental care visits, physiotherapy visits and nursing visits (e.g., wound care in home situation or outpatient visit).

Medical costs consisted of hospitalization, outpatient, and pharmaceutical costs. Out-of-pocket costs and reimbursed costs were analyzed separately. Societal costs consisted of unemployment and medical-related absenteeism costs. The latter was further classified into absenteeism for less than 1 year, in Belgium called 'incapacitation for work', and absenteeism for more than 1 year, called 'invalidity'. Short-term absenteeism (i.e., <1 month for white-collar employees (≈clerical staff) and self-employees, and <14 days for blue-collar employees (≈manual workers)) was not included in the available data as this period is covered by the employer. Societal costs were calculated by multiplying the number of days unable to work with the average cost of absenteeism in Belgium,[13] thus representing the potential productivity gain with full employment. All costs were inflated to 2018 euro values using the Consumer Price Index.[14]

2.4. Statistical analyses

The same epidemiological approach as in a recent paper regarding trends in palliative home care was applied.[15] First, trends in HCU were plotted with descriptive, actual rates per year. Second, direct standardization was applied to adjust for changes in the patient cohort composition during the study period. Standardization was based on age category (i.e., 18-29y, 30-39y, and ≥40y), sex (i.e., men, women), and lesion complexity (i.e., mild, moderate, severe) as defined by Task Force 1 of the 32nd Bethesda Conference.[16] The first year of the study period (i.e., 2006) was used as the base year, and the composition of patient population characteristics (i.e., 18 categories based on age category, sex, and lesion complexity) of that year was kept constant over the entire study period. Then, for each year in the study period, the actual rate of HCU within each of the 18 categories was applied on the base year's patient population distribution to obtain the standardized HCU rate per year:

$$Standardized\ HCU\ rate\ for\ the\ total\ patient\ cohort\ for\ a\ given\ year\ = \frac{\sum \frac{Hct}{Nct}\ x\ Nc2006}{N2006}$$

With Hct = HCU (e.g., number of hospitalizations) in a given category c (e.g., 18-29 year old man with severe lesion) in a given year t (e.g., 2006-2015); Nct: number of patient years in the given category c in the given year t; Nc2006: number of patient years in the given category c in 2006; N2006: total number of patient years in 2006.

The closer the actual and standardized (std) HCU rates were, the less impact possible changes in patient population composition had (or the composition was stable), and the more the trends in HCU were impacted by within-group variation. Conversely, more pronounced differences between the actual and standardized HCU rates suggested a changing patient population composition in terms of age, sex, and complexity.

All data was characterized by a positively skewed distribution. Generalized linear mixed models with log-link function and a negative binomial distribution assessed the impact of time, sex, lesion complexity, and age on count data such as HCU. A Gamma distribution was applied if the dependent variable reflected cost data. Collinearity diagnostics were conducted, and tolerance values of 0.4 or lower were considered to reflect multicollinearity. P-values of ≤.05 were considered statistically significant.

Analyses were performed with SAS Enterprise Guide V.7.1 (SAS Institute Inc., Cary, NC, USA).

2.5. Patient and public involvement statement

Not applicable.

3. Results

A complete overview of results can be found in Supplementary Material.

3.1. Study population characteristics

The patient population increased by 36.6% from 7,408 in 2006 to 10,122 in 2015 (Tab. 1). Mortality rate was low with less than 1% of patients dying each year, but was significantly higher in patients with severe lesions and in age category ≥40yrs. Sex distribution was nearly equal. The average age increased over the study period with 1.6 years to 38.3 years. Patients with mild lesions represented over half of the patient population throughout the study period, but the group of patients with moderate and severe lesions increased proportionally (Fig. 1).

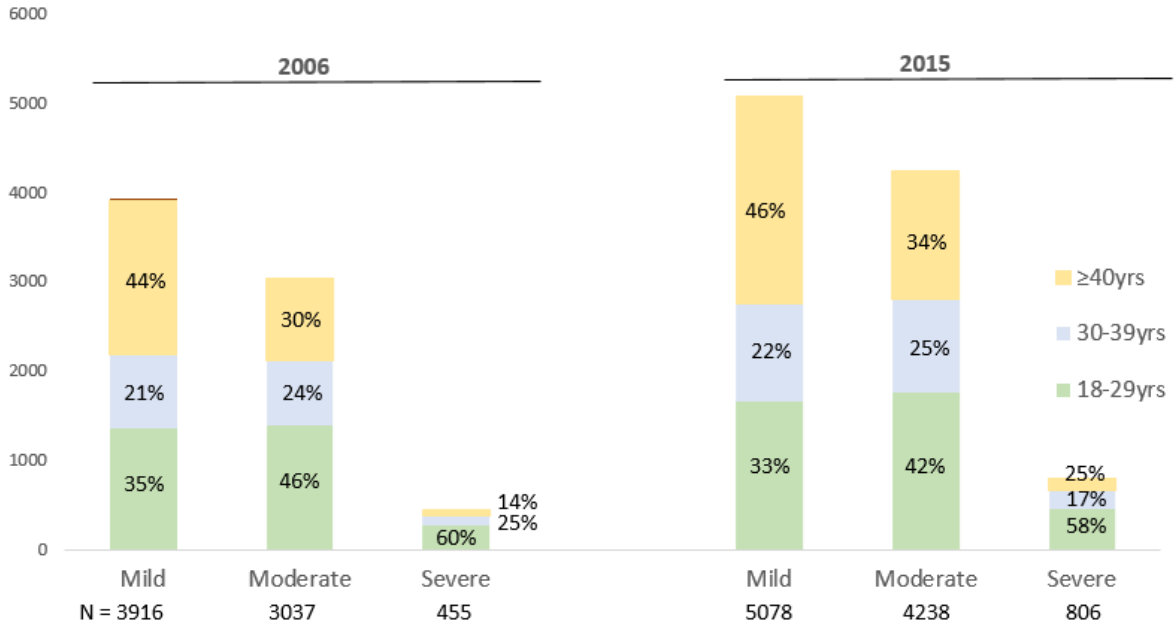

Figure 1: *Demographics, stratified for age and lesion complexity, for the first and last year of the study period.*

Table 1: *Population characteristics (N=10,572).*

		2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of patients		7,408	7,685	7,967	8,292	8,629	8,934	9,236	9,557	9,843	10,122
Number of patient years		7,397	7,667	7,952	8,275	8,610	8,915	9,213	9,540	9,817	10,092
Number deceased*		20	34	33	31	42	35	46	44	54	68
Sex	Women	52.4%	52.4%	52.2%	52.2%	52.1%	52.1%	52.0%	51.9%	51.8%	51.8%
Age in years	Average	36.7	36.9	37.1	37.2	37.3	37.5	37.7	37.8	38.1	38.3
	18-29yrs	41.0%	40.6%	40.0%	39.8%	39.8%	39.5%	39.3%	39.1%	38.5%	38.3%
	30-39yrs	22.4%	22.7%	23.3%	23.3%	23.4%	23.3%	22.9%	23.0%	23.5%	23.2%
	≥40y	36.5%	36.8%	36.7%	36.9%	36.9%	37.2%	37.8%	37.9%	38.0%	38.5%
Lesion complexity	Mild	52.9%	52.5%	52.2%	52.0%	51.6%	51.2%	50.8%	50.6%	50.5%	50.2%
	Moderate	41.0%	41.1%	41.3%	41.4%	41.6%	41.8%	41.9%	41.9%	41.9%	41.9%
	Severe	6.1%	6.4%	6.5%	6.6%	6.8%	7.1%	7.3%	7.5%	7.6%	8.0%

**Mortality was significantly higher in patients with severe lesions compared to patients with mild (Odds Ratio (OR) = 1.67) or moderate (OR = 1.39) lesions.*
Mortality was also significantly higher in patients ≥40y compared to patients 18-29yrs (OR = 5.72) and patients 30-39yrs (OR = 4.32).

3.2. Medical costs

Trends. Medical costs per patient year increased on average 3% per year from €3,490 to €4,536 (std: €4,457). The annual percentage increase appeared to be lower in patients with severe lesions (1.2% per year). Hospitalization, outpatient and pharmaceutical costs accounted for ± 45%, 38% and 18% of the total cost (Fig. 2). Hospitalization costs increased faster than outpatient costs (3.2% vs 2.5% per year).

Determinants. Higher total medical costs were found in older age categories, patients with severe lesions, and women (Tab. 2).

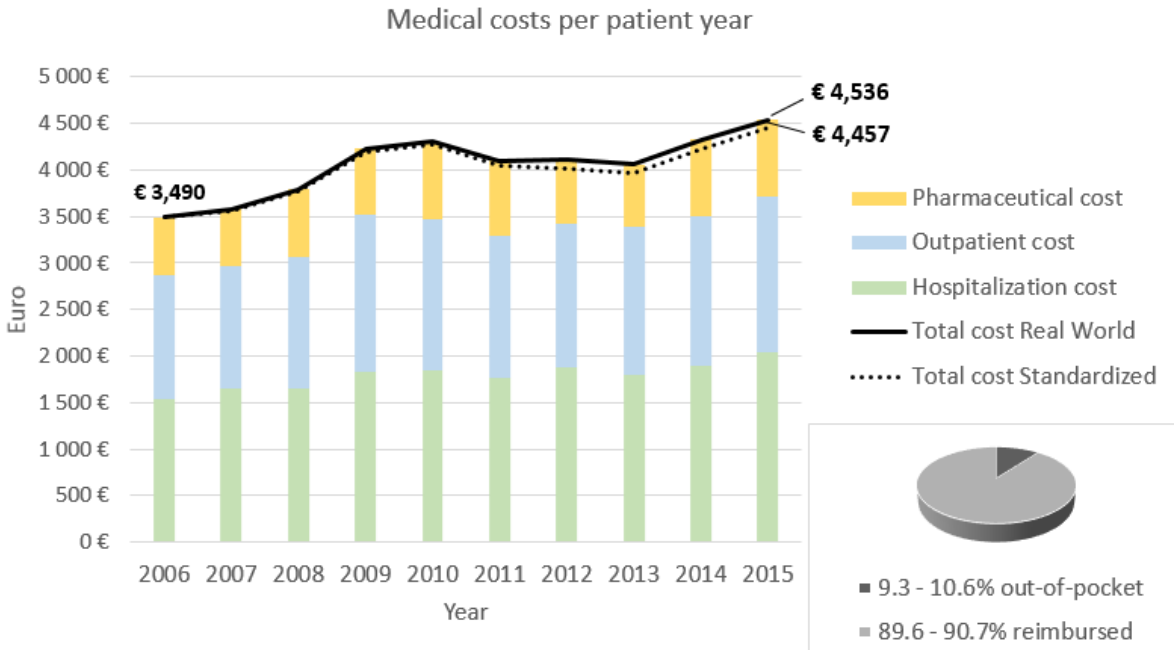

Figure 2: *Medical costs per patient year, stratified for pharmaceutical, outpatient and hospitalization costs. Repartition between out-of-pocket and reimbursed costs.*

Table 2: Generalized Linear Mixed Model with annual outpatient cardiology visits, hospitalization, medical cost, medical absenteeism-related cost, and unemployment-related cost as dependent variables.

	ACHD specialist					General cardiologist					Hospitalization				
Effect	Est.	P-value	% increase	Lower	Upper	Est.	P-value	% increase	Lower	Upper	Est.	P-value	% increase	Lower	Upper
Intercept	-2.43	<.0001				-1.47	<.0001				-1.96	<.0001			
Age 18-29															
Age 30-39	0.10	0.01	11%	2%	20%	0.37	<.0001	45%	36%	55%	0.27	<.0001	31%	23%	40%
Age ≥40	-0.02	0.63	-2%	-11%	7%	0.96	<.0001	160%	143%	179%	0.63	<.0001	87%	75%	100%
Mild															
Moderate	0.95	<.0001	158%	133%	186%	0.45	<.0001	57%	46%	68%	0.05	0.18	5%	-2%	12%
Severe	1.69	<.0001	441%	377%	514%	0.94	<.0001	157%	127%	190%	0.54	<.0001	72%	54%	93%
Men															
Women	-0.01	0.84	-1%	-9%	8%	-0.02	0.48	-2%	-8%	5%	0.20	<.0001	22%	14%	30%
Year	0.06	<.0001	6%	5%	7%	0.03	<.0001	3%	3%	4%	0.02	<.0001	1.7%	1.1%	2.3%
	Medical costs					Medical absenteeism-related costs					Unemployment-related costs				
	Est.	P-value	% increase	Lower	Upper	Est.	P-value	% increase	Lower	Upper	Est.	P-value	% increase	Lower	Upper
Intercept	7.73	<.0001				-1.66	<.0001				-0.46	<.0001			
Age 18-29															
Age 30-39	0.23	<.0001	25%	16%	35%	0.65	<.0001	91%	78%	104%	-0.04	0.29	-4%	-10%	3%
Age ≥40	0.61	<.0001	85%	67%	104%	1.10	<.0001	202%	174%	233%	0.07	0.11	8%	-2%	18%
Mild															
Moderate	0.04	0.52	4%	-7%	16%	0.00	0.97	0%	-12%	14%	-0.09	0.10	-9%	-18%	2%
Severe	0.45	<.0001	57%	28%	92%	0.25	0.03	29%	3%	61%	-0.09	0.35	-9%	-25%	11%
Male															
Female	0.11	0.04	12%	1%	24%	0.27	<.0001	31%	16%	47%	-0.09	0.09	-9%	-17%	1%
Year	0.04	<.0001	4%	3%	4%	0.06	<.0001	6%	6%	7%	0.00	0.54	0%	0%	1%

*Confidence Interval = 95%. Intercept ACHD specialist: e^-2.43 = 0.088 (0.079 – 0.099); Intercept general cardiologist: e^-1.47 = 0.229 (0.212 – 0.248); Intercept hospitalization: e^-1.96 = 0.141 (0.130 -0.153). Intercept medical cost: e^7.73 = €2,267 (€2,039 – €2,515); Intercept medical absenteeism-related cost: e^-1.66*10,000= €1,893 (€1,685 – €2,126); Intercept unemployment-related cost: e^-0.46*10,000 = €6,332 (€5,716 – €7,015). Est. = Estimate.*

*Example: A male patient, 18-29 years old with a mild lesion, in 2006, had an average medical cost of €2,267. A male patient, 30-39 years old with a severe lesion, in 2007 had an average medical cost of €2,267*1.25*1.57*1.04= €4,627.*

3.3. Societal costs

Trends. Fig. 3 shows a 2.0 percent point (p.p.) increase to 7.4% (std: 7.2%) for invalidity while incapacitation for work decreased 0.4 p.p. to 7.9% (std: 7.8%). Absenteeism-related costs per patient year increased 3.2% per year from €6,321 to €8,396 (std: €8,135). The increase was most pronounced in age categories ≥30yrs and patients with mild lesions.

The proportion of patients being unemployed at least one day in a year decreased 3.1 p.p. to 13.8% (std: 13.8%). Unemployment-related costs per patient year decreased 3.5% per year from €7,420 to €5,373 (std: €5,406). The decrease was most pronounced in patients with severe lesions and age category ≥40yrs.

Determinants. Higher absenteeism-related costs were found in older age categories, patients with severe lesions, and women. However, no covariates had a significant impact on unemployment-related costs (Table 2).

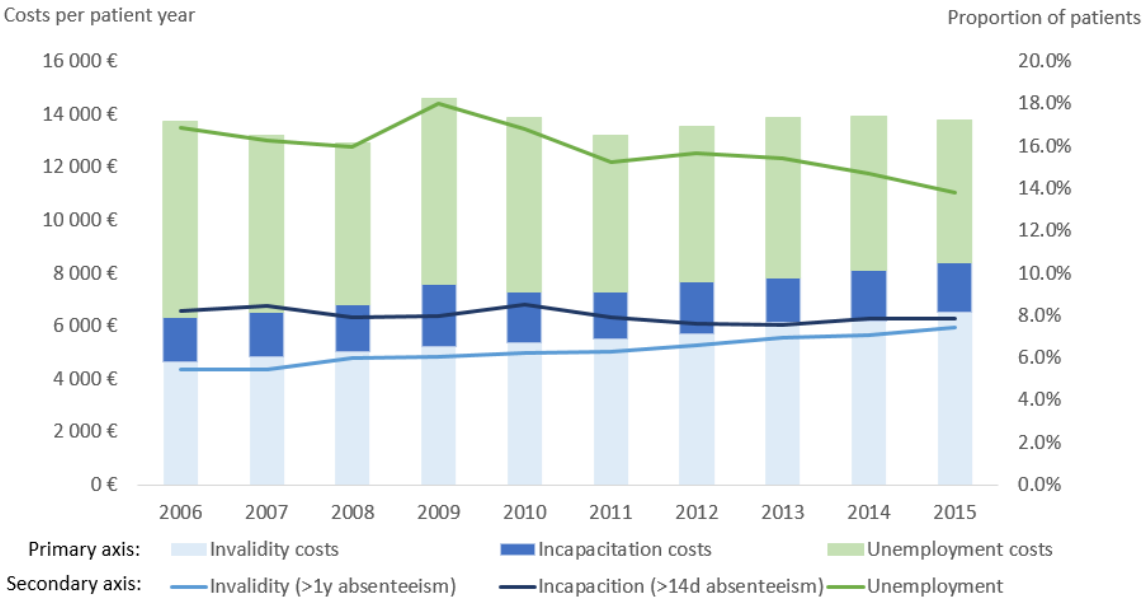

Figure 3: *Bars: real world societal costs related to absenteeism (invalidity + incapacitation) and unemployment. Lines: proportion of patients being unemployed, incapacitated, or invalid for at least one day during a year.*

3.4. Outpatient cardiology visits

Trends. Forty-seven percent of patients visited a cardiologist in 2015, an 11.6 p.p. increase compared to 2006. Particularly, increases in the proportion of patients with at least one visit to ACHD specialists (8.7 p.p. to 21%) and to general cardiologists (6.6 p.p. to 35%) were noted (Fig. 4). In 2015, 81% (+10.9 p.p.) of patients with severe lesions had at least one cardiology visit, and 52% (+12.7 p.p.) had at least one ACHD specialist visit (Figure 5). This all corresponded to an increase in total cardiology visits per patient year from 0.71 to 1.03 (std: 0.98). General cardiology visits were most common, with a 33.8% relative increase from 0.50 to 0.70 (std: 0.67) visits per patient year. Likewise, ACHD specialist visits increased 58.2% from 0.18 to 0.29 (std: 0.27) visits per patient year. The relative increase was strongest in the ≥40yrs age group and in patients with moderate lesions.

Determinants. The ACHD specialist was visited significantly more by age group 30-39, and the general cardiologist by age group ≥40yrs. Higher lesion complexity was related to significantly more visits to all three cardiologist groups. Sex did not have an impact (Table 2).

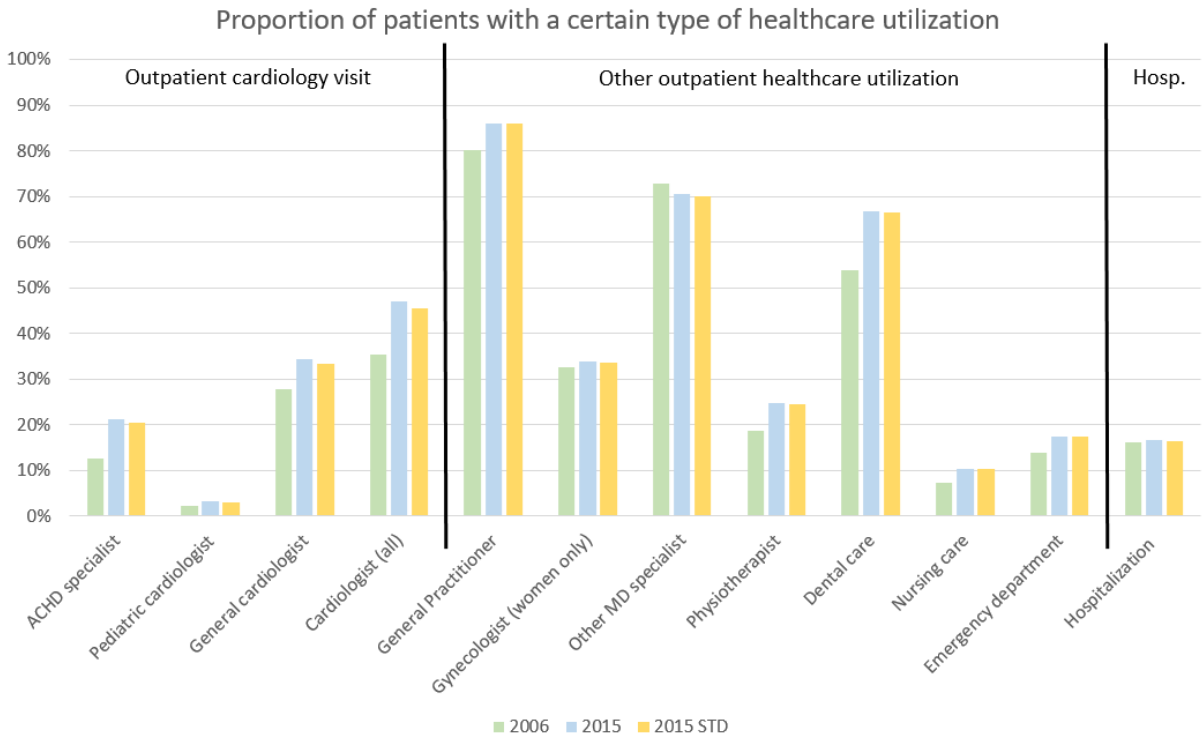

Figure 4: *Real world proportion of patients per healthcare utilization type with at least one encounter. 2006 versus 2015. ACHD: adult congenital heart disease; MD: medical doctor.*

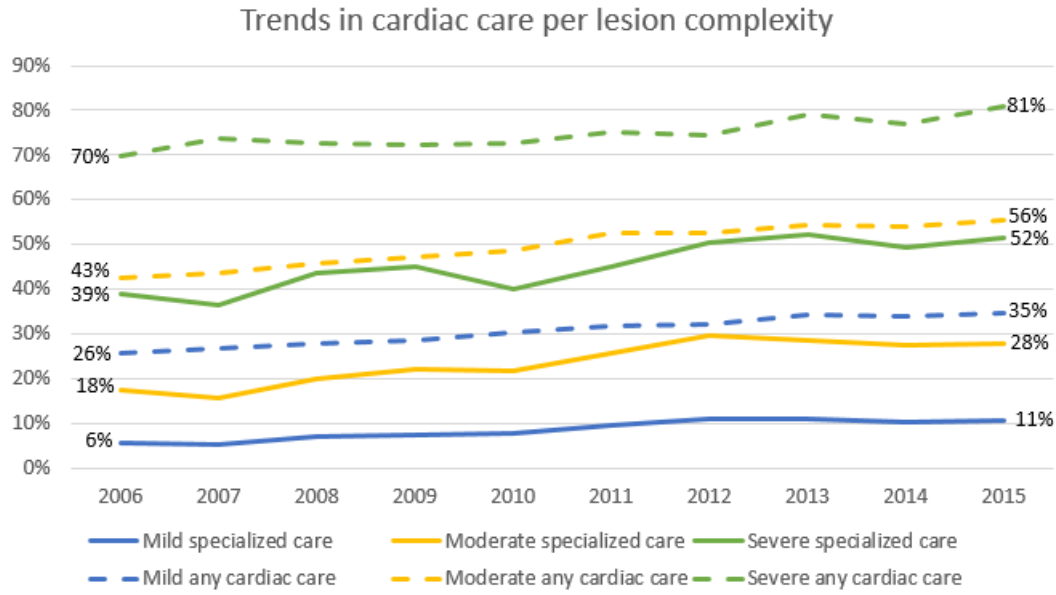

Figure 5: *Proportion of patients with at least one ACHD specialist visit. 2006 to 2015, per year, stratified for lesion complexity.*

3.5. Other outpatient HCU

Trends. The annual percentage of patients with at least one outpatient visits to a particular health professional increased over time, expect for visits to other MD specialists (Fig. 4). This corresponded to a respective 101.7%, 49.6%, 15.2%, 7.1%, and 39.7% increase of nursing care visits, physiotherapist care visits, dental care visits, gynaecology visits, and ED visits per patient year.

Determinants. The impact of age and lesion complexity varied across types of HCU, but overall, women appeared to incur significantly more HCU.

3.6. Hospitalization

Trends. The annual hospitalization rate remained stable over time with 16-17% of patients being hospitalized (Fig. 4). The number of hospitalizations per patient year however increased with 11.7% from 0.24 to 0.27 (std: 0.26), and average LOS per hospitalization increased from 9.57 to 10.20 days (std: 10.18). Importantly, such an increase was only noticed in patients with mild or moderate lesions: decreases in hospitalization rate from 0.37 to 0.31 and in LOS from 7.8 to 7.4 days were found in patients with severe lesions.

Determinants. Hospitalization rate was 72% (54-93%) higher in patients with severe lesions compared to patients with mild lesions. LOS did not differ significantly for lesion complexity. Age categories 30-39 and ≥40yrs were associated with respectively 31% (23-40%) and 87% (75-100%) more hospitalizations. Women were 22% (14-30%) more hospitalized than men with a 14% (3-24%) shorter LOS (Table 2).

4. Discussion

This longitudinal, multi-center cost-of-illness study made use of a retrospective database linking administrative and clinical data. This study demonstrated substantial increases in per patient year medical and absenteeism-related costs, while a decrease in unemployment-related costs was observed. The standardized values, adjusting for the ageing and more complex patient population, mitigated the increase in medical and absenteeism-related costs to a limited extent. In other words, there would have been a slightly smaller cost increase if the patient population composition had remained stable over time.

Medical costs. The percentage increase in medical costs over time is higher in patients with mild or moderate lesions compared to patients with severe lesions. Possible explanations are a higher age of the group with mild to moderate lesions causing a faster increase in comorbidities, a suboptimal fit between care needs and care received, technological evolution,[3] or simply because patients with severe lesions already incurred high costs before and had an increased mortality rate. A previous study on medical costs in Belgium was conducted back in 1997.[17] Adjusted for inflation and after exclusion of pharmaceutical costs (not all pharmaceutical costs were included), medical costs did not increase between 1997 and 2006 while our results showed a 29% increase between 2006 and 2015. This older study was correctly framed as a pilot study because, apparently, a selection bias (only patients seen by an ACHD specialist were selected) led to an excessively high cost estimate. For example, the hospitalization rate in that study was substantially higher.[17] Nonetheless the limitations for this comparison, it seems that costs were accelerating more recently. The acceleration was driven by strong increases in outpatient HCU while the hospitalization rate per patient year increased with a slower slope. However, the acceleration was also driven by the increasing cost per hospitalization which could be explained by a longer LOS,[18] and more disease burden related to an ageing patient population over time.[18, 19]

Societal costs. Only one previous (US) study calculated the productivity loss cost following hospitalization.[9] In our study, we calculated the productivity loss cost, covering absenteeism and unemployment. The societal costs of adults with CHD appeared to be higher than their medical costs. Note that only part of these costs could be attributed specifically to the ACHD pathology as absenteeism and unemployment are prevalent in the general population as well. Unemployment and invalidity were the most important cost components of societal costs, with an increasing importance of invalidity-related costs. Invalidity appeared to become more prevalent over time, similar as in the general population.[20] General explanations are medical progress leading to better survival, an increasing labour market participation, and policy measures such as a higher retirement age.[21] Invalidity in the ACHD population was higher compared to the general population (7.4% vs 5%) despite the fact that invalidity normally occurs more often after the age of 50[20] while our ACHD cohort was relatively young. Unemployment (-related costs) decreased, while it remained stable between 2006 and 2015 and only decreased after 2015 in the general population[22], offering positive prospects. Recent research demonstrated lower unemployment and invalidity rates in Belgium compared to other countries.[8] Hence even more pressing societal costs may be encountered elsewhere.

Outpatient cardiology visits. Less outpatient cardiology visits of patients with mild lesions were counted compared to previous European studies, whereas comparable rates were found for patients with moderate and severe lesions.[19, 23] One in five patients with severe lesions had no cardiac follow-up in the last year of the study period, but increasing numbers of patients were receiving specialized care while hospitalization rates decreased. Furthermore, general cardiologist visits remained more prevalent in patients with mild and moderate lesions and in patients ≥40yrs. In light of the results of Mylotte et al.[24] and Cordina et al.[25], who demonstrated clinical benefits following ACHD specialist visits, special attention should be given to guide patients towards specialist care. However, more research is needed to settle the debate about shared care for patients with mild and moderate lesions.

Other. Other outpatient HCU in this study is higher than in the Dutch study from Schoormans et al.[7] (e.g., >80% vs 40% of patients visiting a GP in the course of a year). Next to healthcare system differences, research aim dissimilarities can provide an explanation for these differences. Schoormans et al.[7] assessed cardiac disease-related outpatient visits only, whereas we assessed outpatient visits indifferent of cause. Our longitudinal analyses revealed increases in most types of HCU which were more pronounced in patients with mild and moderate lesions. This is in line with the results obtained for outpatient cardiology visits (in this and in previous research[24]): patients with mild and moderate lesions are older, causing a more pronounced increase in HCU. One important type of HCU is dental care to prevent infective endocarditis.[26] Annual visits are highly recommended for many patients with ACHD. An increase in dental care has been noticed throughout the study period, resulting in 67% of the patients receiving dental care in 2015. This is substantially lower than what has been found in a recently published self-reporting study (86% in Belgium),[27] suggesting a self-reporting bias, and warranting continued patient education. Dental care in adults with CHD is, however, better than dental care in the general population (±50%).[28]

Sex. Previous literature on sex disparities remained inconclusive even though there seemed to be a tendency for more HCU in women.[3] This study strengthened the thesis of higher medical costs in women although the cost per hospitalization was higher in men. Several explanations can be put forward to explain this disparity such as the impact of pregnancy management and –related hospitalization.[29] Previous research also suggested that, overall, women experience fewer barriers to make use of available healthcare services subsequently leading to a lower need for long-term inpatient care.[30]

4.1. Limitations

First, the retrospective data were not primarily gathered to answer specific research questions.[31] We were for example not able to specifically determine details of the hospitalizations such as the medical department in which the hospitalization took place. Administrative databases are also prone to miscoding and missing data.[31] However, retrospective database research is a low-cost solution to include a big sample size, which counters small numbers of miscoded and missing data.[31] Second, the BELCODAC is built on all ACHD patients affiliated to both Flemish tertiary centers. From a third center, only patients with severe lesions were included. However, the oversampling of patients with severe lesions does not impede generalization because the patients included from the third hospital accounted for <2% of included patients. Third, we did not analyze HCU for specific congenital anomalies separately. For example, we did not analyze different mild lesions separately despite possible differences in HCU.[3] Fourth, our calculation did not include HCU that cannot be reimbursed. For example, adult psychotherapy is only reimbursed in some rare cases, and is therefore only partly included in our analyses.

4.2. Conclusion

Despite some limitations, this study has important added value because, to date, no comprehensive cost-of-illness research had been conducted in the ACHD population. The importance and applicability of cost-of-illness studies for clinicians and policy makers is multifold as it can help determining the most appropriate care level, populate cost-effectiveness models, and inform about future budget impact. This study demonstrated increased access to specialized cardiac care, less unemployment, and more long-term invalidity. Overall, the medical cost increase is most pronounced for patients with mild or moderate lesions, probably related to their higher age.

5. Declarations

5.1. Acknowledgements

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5.2. Funding statement

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5.3. Competing interests

None to declare.

5.4. Availability of data and materials

Not available.

5.5. Ethical approval

The study was approved by the privacy commission (SCSZG/17/184) and the ethical committees of the participating hospitals (S59858, B670201731994, 2017/26JUI/332).

5.6. Contributions

RW, JDB, and LA designed the study protocol. RW analyzed the data and wrote the manuscript draft. All authors contributed substantially to the construction of the database, the conceptualization and design of the manuscript, revised the manuscript critically for important intellectual content, and approved the manuscript to be submitted.

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