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4 **SOCIETAL PERSPECTIVE OF COST ANALYSIS**
5 **OF AN EARLY INTERVENTION PROGRAMME**
6 **FOR AUTISM CHILDREN AND**
7 **ITS CONTRIBUTING FACTORS IN KLANG**
8 **VALLEY MALAYSIA, 2019**
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13 **ABSTRACT**
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Autism spectrum disorder (ASD) is a public health concern globally, characterized by impairments in cognitive process, social functioning, communication skills, behaviours and interests. These problems require a multidisciplinary approach through an early intervention programme (EIP) which is remarkably expensive. To date, the knowledge of EIP costs for ASD children in Malaysia remains unknown. This study estimated the annual average costs of EIP for ASD children from the societal perspective (total average costs, education costs, treatment costs, and living costs), the relationship between the total annual average costs of EIP and its predictors. A cross-sectional cost analysis study using simple random sampling according to proportion was conducted among 280 parents of ASD children receiving EIP services in Klang Valley. The data were collected using interview-based questionnaire and proforma. The Activity-based Costing Technique was used to estimate the EIP-related costs. The non-parametric test was used for bivariate analysis and multiple linear regression for the predictors. The result showed that the total annual average costs of EIP, average education costs, average treatment costs, and average living costs per ASD child were estimated at RM15,158; RM3,896; RM1,948; and RM4,409 respectively. There was a significant association ($P = .05$) between total annual average costs of EIP, and its contributing factors; family income, ASD level, programme characteristics, and family support. Multiple regression analysis showed that 27% of the total annual average costs of EIP can be predicted by the combination of these factors; EIP types, EIP frequency, centre-based type, ASD level and family income. In conclusion, the study determined the total annual average costs of EIP and its predictors. This information is beneficial as evidence to assist the decision on future resource allocation by the policy maker.

15
16 *Keywords: cost-analysis, total annual average costs, education costs, treatment costs, autism spectrum disorder, early*
17 *intervention programme*
18

19 **1. INTRODUCTION**
20

21 Autism spectrum disorder (ASD) is a public health concern globally with increased prevalence over the last decade [1]. As
22 one of the commonest developmental disability affecting children worldwide [2][3], ASD is characterized by impairments
23 and restrictions in cognitive process, social functioning, communication skills, behaviors and interests [1][4][5]. The term
24 "spectrum" reflects the wide variation in challenges and strengths possessed by each child with ASD. These problems
25 mandated multidisciplinary assessment and management by a multidisciplinary team consisting of family medicine
26 specialist, pediatrician, psychiatrist (child and adolescent), psychologist (clinical and educational), counsellor,
27 occupational therapist, speech-language therapist, medical social worker, and education officers [6].

28
29 In managing ASD cases, an early intervention programme (EIP) is an important intervention to determine the magnitude
30 of disease outcomes in term of cognitive, behavioral and social adaptability [6][7][8]. EIP should be offered to all children
31 diagnosed with ASD as early as 36 months old to improve the outcomes. The models of EIP included home-based or
32 centre-based program[9]; which involved integration of physical therapy, speech and language therapy, occupational
33 therapy, psychological therapy, behavioral therapy, special education, social welfare and medical interventions[6][10].To
34 achieve the best outcome for children with ASD across lifespan, EIP can be one of the alternatives[11].

35
36 Regarding ASD's assessment, diagnosis and treatment, it requires comprehensive, intensive and multisectoral
37 management approach[6][10]. Since it requires a multisectoral approach, EIP is a crucial component and it is very
38 expensive [12]. Studies from developed countries such as United Kingdom and United States showed that, the total
39 average costs of managing a child with ASD in a lifetime ranged from RM4.4 million to RM5.9 million [13]. However, the
40 specific information on the total annual average costs of EIP per ASD child remains unknown in a centre-based EIP in
41 Malaysia, as no study has been done before. Knowledge on average costs of programme (including average costs of EIP)
42 is important for policy development and resource distribution[9][14][15].

43
44 The study was carried out to answer the question of what the annual average costs of EIP per ASD child (total average
45 costs, education costs, treatment costs, and living costs) and its predictors in the centre-based EIP in Klang Valley,
46 Malaysia from the societal perspective.

47 48 **1.1.EPIDEMIOLOGY OF ASD**

49
50 Based on epidemiological studies conducted over the past 50 years, the prevalence of ASD appears to be increasing
51 globally, due to increase in screening tools with more detailed criteria of the Diagnostic and Statistical Manual of Mental
52 Disorders (DSM) IV, which allow more comprehensive coding of the prevalence data. In a recent estimate by the World
53 Health Organization (WHO), prevalence of ASD was estimated at 1 in 160 children[16]. The prevalence of ASD in the
54 United States has increased tremendously over the past 5 years with a rate of 16.8 per 1,000 (1 in 59) children aged 8
55 years in total [17]. In Malaysia, there is no official registry system available to monitor epidemiological data on the
56 prevalence of ASD at present. However, a smaller scale study by the Ministry of Health on children between the ages 18
57 to 36 months showed a rate of 1.6 in 1000 children, or approximately 1 in 625 children[18][6].In terms of cognitive
58 impairments, about 30% to 50% of children with ASD were estimated to have intellectual disability with IQ below 85 and
59 have poorer adaptive behavior that contribute to ineffective social communication[19].As indicated in the available
60 scientific evidence currently, environmental and genetic factors were involved with development of ASD, and no clear
61 evidence of a causal relationship between measles, mumps and rubella vaccine, and ASD [11][16]. Older parents are at a
62 higher risk to have children born with ASD, and parents who have ASD child have a 2 to 18 percent chance of having a
63 second child who would be affected by ASD [11].

64
65 An individual with ASD has limited capacity to perform daily works and have difficulties to participate in society, because
66 of poor communication skills that may affect their educational and social attainments as well as employment opportunities.
67 While some individuals with ASD can live independently, others have severe disabilities and require life-long care and
68 support [5]. The children with ASD and their families may experience significant emotional and economic burden, by
69 which children with more severe ASD require strong support for services accessibility and intensity. In the United States
70 and United Kingdom, the lifespan costs to support a child with ASD was estimated at RM5.9 million and RM4.4 million,
71 respectively [13]. Notwithstanding, with the presence of intellectual disability, higher costs were expected. Regarding
72 medical expenditure, children with ASD incurred 4.1 higher cost compared to those children without ASD and it was
73 expected to be increased exponentially following the rise in prevalence for the next decade, without an effective
74 intervention[11]. In Malaysia, the total economic costs experienced by parents was estimated at RM35,365 per year[10].

75 76 **1.2.REVIEW OF FACTORS CONTRIBUTING TO ASD-RELATED COSTS**

77
78 A systematic review was conducted alongside with the research development to comprehensively assess the factors
79 contributing to the EIP-related costs for ASD children. The systematic search was conducted based on the research
80 question on what are the contributing factors of the average cost of EIP among ASD children. The objective of the review
81 was to identify the average costs of EIP among ASD children from various sources.The search was conducted through
82 electronic database Ovid MEDLINE® from 1946 to November 16, 2018 using the combination of Medical Subject
83 Headings (MeSH) keywords and its related scopes available as follows; "Autism Spectrum Disorder" or "Autistic Disorder"
84 and "Early Intervention (Education)" or "Early Medical Intervention" and "Costs and Cost Analysis". General search engine
85 was used through Google Scholar to search for additional related articles using similar keywords combination.The
86 detailed information on keywords and their combination was tabulated in **Appendix 1**.The search exercise was focused on
87 the economic evaluation studies pertaining to ASD and its intervention, full text articles, scholarly journals and English

88 articles that were published for the past 20 years. After selection, checking for duplicates, and hand search, 15 articles
89 were finally selected, and their contents were then reviewed (see **Appendix 2**–The search process according to PRISMA
90 guideline). Two review authors extracted data independently from each study regarding type of study, type of intervention,
91 year of publication, journal, outcomes of the study, and the location of study. The quality of the reviewed articles was not
92 further assessed as the credit of journals was considered enough. Based on the medical model of health determinants
93 adapted from Dahlgren and Whitehead (1991) framework, the retrieved factors were categorized into sociodemographic
94 factors (age of child, family income, residence location), medical condition factor (ASD level), health service factors
95 (centre-based type, programme characteristics), and environmental factors (family support, EIP centre distance). The
96 summary of results on factors contributing to ASD costs was tabulated in **Appendix 3**.
97

98 **1.3.COSTS CONCEPT**

99
100 The cost concept is defined as the analysis of comparative costs of alternative treatments or health care programmes. A
101 costing exercise starts with the formation of a well-defined decision problem, including the objectives of costing, the
102 perspective of costing, and the time horizon, as well as the description of a service. The perspective for an analysis may
103 be that of a specific provider or providing institution, the patient or groups of patients, a third-party payer (public or
104 private), or a broad perspective (i.e. all costs and consequences to whomsoever they accrue). After the service for costing
105 has been defined in detail, the costing methodologies follow three distinctive steps: the first step is identification of
106 resources used to deliver the service, second is the measurement of resource utilization in natural units, and the third
107 one is attaching monetary value to resource used[20].
108

109 **1.4.COSTING METHODOLOGY**

110
111 The common costing methods used in healthcare, are the traditional step-down approach (macro-costing), micro-costing
112 and activity-based costing (ABC). Macro-costing is a top-down approach, it involves the process of allocating overhead
113 cost to the departments or the units of services based on service volume to estimate the average unit costs. Micro-costing
114 approach involves the collection of data about resource use by each individual service (item-by-item and line-by-line). This
115 bottom-up approach can be used where the accuracy of resource measurement is important, contingent on data
116 availability, and whether it is feasible in an economically sensible way. Micro-costing is the most precise estimation
117 compared to the traditional macro-costing approach, which is based on average estimation including case-mix, disease
118 cost per diem and average cost per diem. The ABC method involves the step-down approach at first. Next, the shared
119 activities need to be identified (activity-centre) and the total cost will be allocated down to the departments in proportion
120 according to their consumption of resources (cost driver). The department costs will then be divided into its service
121 volume to estimate the unit costs. The cost calculated will be the average cost and presented as average cost per contact
122 point or per visit or per service[20].
123

124 **2. METHODOLOGY**

125
126 A cross-sectional costs analysis study using simple random sampling according to proportion was conducted among 280
127 parents of ASD children receiving EIP services in the Klang Valley, which include government and non-government EIP
128 centres. Parents of all ASD children aged less than 7 years old which enrolled in EIP centres in the Klang Valley were
129 included, and those ASD children with other co-morbidities were excluded from the study. The required sample size was
130 calculated according to the hypothesis testing formula for two groups by Lemeshow et al. (1990). To get an adequate
131 sample unit from the sampling frame, 2 government and 2 non-government EIP centres that match the centre-based
132 criteria were selected using the lottery method. The data on contributing factors were collected using interview-based
133 questionnaire and a proforma was used to obtain the data on EIP-related costs. The research instrument was administered
134 and retrieved personally by the researcher. The instrument for the study was submitted to health economics experts
135 for validation. The Cronbach's Alpha and Intra-Class Correlation were used to determine the reliability of the instrument.
136 Both descriptive and inferential statistics were performed. The relationship between the total annual average cost of
137 EIP and its predictors were carried out using non-parametric tests.
138

139 The cost components included were the direct costs for EIP-related intervention. The indirect costs such as parents'
140 productivity loss, time-off work, and opportunity cost were excluded from the estimation. The provider costs (including
141 capital, staff, utilities, maintenance) were estimated using an ABC method that estimates the total annual average costs of
142 EIP according to the proportion of resources allocated for EIP services. The patient cost was estimated from the reported
143 annual out-of-pocket expenditure (OOP) by the parents, and the breakdown of cost was estimated based on the
144 proportion of annual OOP for ASD-related intervention[21]. From the societal perspective, the total annual average costs
145 of EIP in each centre were estimated using the formula as follows:
146

$$\frac{\sum(\text{Capital}^1 + \text{staff}^2 + \text{utilities}^3 + \text{maintainence}^4 + \text{patient})}{\text{Total number of enrolled ASD patients}}$$

¹costs of building and asset

²salary and allowances for the multidisciplinary team and administrative officers

³electrical bills, water bills, internet bills, phone bills, security services

⁴cleaning services, laundry, water filter, waste management

3. RESULTS AND DISCUSSION

In this study, the overall response rate was 93.3%.The distribution of continuous variables was determined statistically.The Shapiro-Wilk test was significant ($P = .05$) for all continuous variables, showing the data is not normally distributed.Thus, the non-parametric tests were used to determine the relationship between the contributing factors and the study outcome.

3.1. DESCRIPTIVE STATISTICS

The components of descriptive statistics were specified in **Table 1**. The median age of ASD children was 37 months old, Interquartile range (IQR) (30,48). The range of children's age was 69 months with the youngest at 15 months old and the oldest at 84 months old. In general, EIP services were provided by most EIP centres among preschool age group of ASD children, because EIP is believed by many to be most effective when provided at an early age [8][10]. In Malaysia, the EIP service provision in the public centre-based was limited to the preschool age to date, and most EIP centres were concentrated in urban areas because demand for services is higher compared to the rural areas. The gender for both male and female were not equally distributed with the percentages being 85.3% and 14.7% respectively. The finding corresponds with the global prevalence of ASD that showed males are four times more likely to be diagnosed with ASD than females [11][17]. The family income distribution shows that 79.8% of the respondents were earning less than RM100,000 per year.The distribution of ASD severity among respondents' children was defined by the level of support, according to the Clinical Practice Guidelines (CPG) Malaysia, (2014) which adopted the DSM-IV criteria. The severity of ASD was categorized into three level; Level 1 (Requiring support), Level 2 (Requiring substantial support) and Level 3 (Requiring very substantial support). The data on parent's support was retrieved during parents' interview on sharing their experience in handling and managing ASD children in the public and community activities. The reported support level for ASD children, mostly fall within the category of Level 1 and 2 ASD (88.7%), followed by a small portion of ASD children within Level 3 (11.3%).

The features of health services involved the types of EIP consumed, programme intensity (EIP frequency and duration), and centre-based type. As a multidisciplinary approach intervention, EIP incorporated various types of interventions such as Applied Behavioural Analysis (ABA) therapy, speech therapy, occupational therapy, sensory integration and music therapy[6].The finding shows that 76.9% of respondents' child received more than 1 EIP types per session, 53.8% received more than 2 EIP sessions per week and 58% received more than 5 hours of EIP sessions per week. Around 60.9% of ASD children received EIP at a public EIP centre. Regarding the distance of EIP centre, 51.3% of the respondents stay near (less than 20km). The range of the nearest and the farthest EIP centre distance was 60km. In assessing EIP-related services,home relocation was reported by 29.8% of respondents due to logistic reasons such as change to a new workplace that was near to the EIP centre, moving to a house nearer to the EIP centre and other reasons.

Table 1. Descriptive statistics of the factors contributing to the total annual average costs of EIP(N=238)

Variables	n	%
Age Group		
12-23	10	4.2
24-35	77	32.4
36-47	70	29.4
48-59	48	20.2
≥60	33	13.9
Gender		
Male	203	85.3
Female	35	14.7
Average annual income		
< 25000	76	31.9
25000-49000	43	18.1

50000-74000	36	15.1
75000-99000	35	14.7
≥ 100000	48	20.2
ASD level		
Level 1	143	60.1
Level 2	68	28.6
Level 3	27	11.3
EIP types		
1 type	55	23.1
2 types	101	42.4
3 types	60	25.2
4 types	20	8.4
≥ 5 types	2	0.8
EIP frequency		
1 - 2 sessions/week	110	46.2
3 - 4 sessions/week	56	23.5
5 - 6 sessions/week	46	19.3
7 - 8 sessions/week	9	3.8
≥ 9 sessions/week	11	4.6
EIP duration		
< 5 hours/week	100	42.0
5 - 9 hours/week	51	21.4
10 - 14 hours/week	33	13.9
15 - 19 hours/week	20	8.4
≥ 20 hours/week	32	13.4
School type		
Private	93	39.1
Public	145	60.9
School distance		
Near < 20 km	122	51.3
Far	116	48.7
Home relocation		
No	167	70.2
Yes	71	29.8

3.2. ESTIMATION OF TOTAL ANNUAL AVERAGE COSTS OF EIP

The summary of the total annual average costs of EIP from the societal perspective can be seen in **Table 2**. The detailed information on cost estimation for each category was tabulated in **Appendix 4**. The component of staff emolument is the highest burden estimated for the total annual average costs of EIP from the provider perspective (75% to 95%).

Table 2. The estimation of total annual average costsof EIP from societal perspective(N=238)

EIP centre	Staff ¹ (RM)	Utilities ¹ (RM)	Maintenance ¹ (RM)	Building ¹ (RM)	Education ² (RM)	Treatment ² (RM)	Living ² (RM)	Total ³ (RM)
Centre 1	3,371.88	135.91	148.65	858.81	1,839.20	919.60	2,081.20	9,355.25
Centre 2	5,425.00	64.00	70.00	404.42	6,992.00	3,496.00	7,912.00	24,363.42
Centre 3	4,368.00	56.32	61.60	187.17	2,574.50	1,287.25	2,913.25	11,448.09
Centre 4	4,352.40	53.46	58.47	-	4,180.00	2,090.00	4,730.00	15,464.33
Average*	4,379.32	77.42	84.68	362.60	3,896.43	1,948.21	4,409.11	15,157.77

¹Average annual costsof EIP per ASD child (provider perspective)

²Average annual costsof EIP per ASD child (patient perspective)

³Total annual average costs of EIP per ASD child from each centre

*Average costs of EIP per ASD child from 4 EIP centres in Klang Valley

The total annual average costs of EIP, education costs, treatment costs, and living costs per ASD child were estimated at RM15,158; RM3,896; RM1,948; and RM4,409 respectively. The estimated total annual average costs of EIP per ASD child in selected government EIP centres ranged from RM 9,358 to RM24,384, and from RM11,437 to RM15,458 for non-government EIP centres. Centre 1 shows the lowest cost estimate because it is partially sponsored by the government. In

contrast to Centre 2, the highest costs were due to lower student staff ratios (1 EIP staff to 4 ASD children) compared to other centres with higher ratios (1 EIP staff to 6 ASD children). In addition, Centre 2 adopted the university hospital financial structure under the Ministry of Education. Higher cost estimates for non-governmental EIP centres have been expected as they involve profit-related components (Centre 3 and Centre 4).

In this study, the estimated amount is very much lower compared to the findings reported in other countries, apart from the currency exchange rate (Table 3). In the Netherlands, the outcome of interest is the societal cost of childhood ASD and the relationship between state and family OOP expenditure. The cost estimation was 15.5 times higher compared to the current study, because the bottom-up prevalence-based cost-of-illness methodology was adopted from a societal perspective. The cost of special needs assistants and the parent's time-off were incorporated in the cost estimation. Similar study incorporated the cost estimation from an older age-group, of which 2 to 18 years old ASD children were involved, and mostly received private ASD-related care services[21].

Also, higher cost was demonstrated in Egypt because home-based EIP was practiced widely as an intervention of choice, due to limitation of an EIP-related services by the state provider[12]. In view of the above, the parent's involvement in providing EIP as a home-based programme was estimated as the full time equivalent (FTE) cost per hour based on the salary rate of EIP staff in centre-based setting. The cost parameters were estimated solely based on the home-based EIP resource utilization by ASD child's family. In the above study, the total estimated cost was mostly influenced by staff cost due to low staff to student ratio observed in the home-based EIP, of which 1 private therapist to 1 ASD child ratio per home EIP session existed.

In Australia, a cost analysis study was conducted to compare the expenses between families with immediate ASD diagnosis following an identification of atypical neuro-developmental delay with families that experienced a delay between first identification and ASD diagnosis. The estimated total ASD-related cost was 12.6 times higher compared to the current study, because the components of treatment-related travel cost, family productivity loss and medical costs were included in the cost estimation, apart from the ASD-therapeutic cost. The total average cost of ASD-related treatments from this study were contributed mainly by loss of income of the parents and caregivers (89%), followed by ASD-related travel costs (3%) and treatment costs (8%)[22].

The cost estimation in both UK and US was 3 to 4 times higher compared to the current study. In UK, the ASD-related treatment costs were estimated by the accumulation of more comprehensive cost components including medical, nonmedical, and indirect economic and lifetime costs [13]. Similar approach was demonstrated in US, whereby an extensive cost component was incorporated in the cost estimation including health care, education, ASD-related therapy, family-coordinated services, and caregiver time [15]. The above study measures the annual utilization and costs for health care, EIP centre services, ASD-related therapies, family-coordinated services, and caregiver time. More cost components incorporated to estimate an economic cost of ASD-related care services. For an instance, the healthcare utilization cost for ASD included were hospitalizations, office and emergency department visits, home health care, dental care visits, and prescription drug use.

Table 3. Comparison of total annual average cost of EIP with other countries (N=238)

Country	Study	Average EIP cost* (RM)	Comparison (times higher)
Netherland	[21]	202,367.22	15.50
Egypt	[12]	169,476.99	12.98
Australia	[22]	164,584.28	12.61
United Kingdom	[13]	54,776.09	4.20
United States	[15]	42,253.85	3.24
Klang Valley, Malaysia	Present study	15,157.77	-

*Estimated annual cost per ASD child; adjusted with 3% discounting; all values converted to Ringgit Malaysia (RM) currency as at November 2018 (1USD=RM4.19, 1GBP= RM5.35, 1EUR=RM4.71)

In this study, the component of patient cost is the highest burden estimated for the total average EIP cost (67.6%), followed by other cost components (Table 4). This finding was expected considering the substantial level of support required from the family in managing ASD-related disabilities, including direct and indirect costs incurred for EIP-related services, such as EIP fees, transportation, time allocated and other opportunity costs. From the perspective of the EIP service provider, the staff cost is the highest burden identified, apart from the patient cost. Similar findings were reported in the US, UK and Australia, by which the multisectoral approach that have a multidisciplinary staff involved in the EIP centre were the biggest contributor to costs associated with ASD [9][15]. The finding accounted for 60%-80% of EIP's programme cost, due to the increased use of multi-therapies and special education services. In estimating the future

burden on EIP cost, we performed the deterministic sensitivity analysis to test the robustness of cost analysis towards multiple parameters within the base value (average EIP cost per ASD child in 2018); to check the extent of the possible economic impact of current cost analysis. The finding shows similar trend with more than 60% of average EIP cost was contributed by the staff emoluments.

Table 4. Comparison of total annual average cost of EIP with other countries (N=238)

Cost categories	Average EIP cost* (RM)	Proportion	Perspective (%)
Staff	4,379.32	28.9%	Provider (32.4%)
Utilities	77.42	0.5%	
Maintenance	84.68	0.6%	
Building	362.60	2.4%	
Education	3,896.43	25.7%	Patient (67.6%)
Treatment	1,948.21	12.9%	
Living	4,409.11	29.1%	

3.2.4. SENSITIVITY ANALYSIS

The Deterministic Sensitivity Analysis (DSA) was done to test the robustness of the conclusions, by determining how the values of cost parameters impact the total annual average costs of EIP in the next 5 years under a set of assumptions as follows; fixed number of students in EIP center, fixed number of EIP staff, fixed EIP programme structure, and 3% discounting applies for the next 5 years. DSA was performed towards multiple parameters within the base value (total annual average costs of EIP per ASD child); to check the extent of the possible economic impact of current cost analysis. A Univariate SA was conducted to assess the parameters by varying $\pm 25\%$ of the base value (**Figure 1**). The DSA shows that the total annual average costs of EIP is most sensitive towards the living costs, staff cost, and education costs compared to others (about 14% to 15% positive incremental following increase 25% of the base values, and 7% to 10% negative incremental following decrease 25% of the base values).

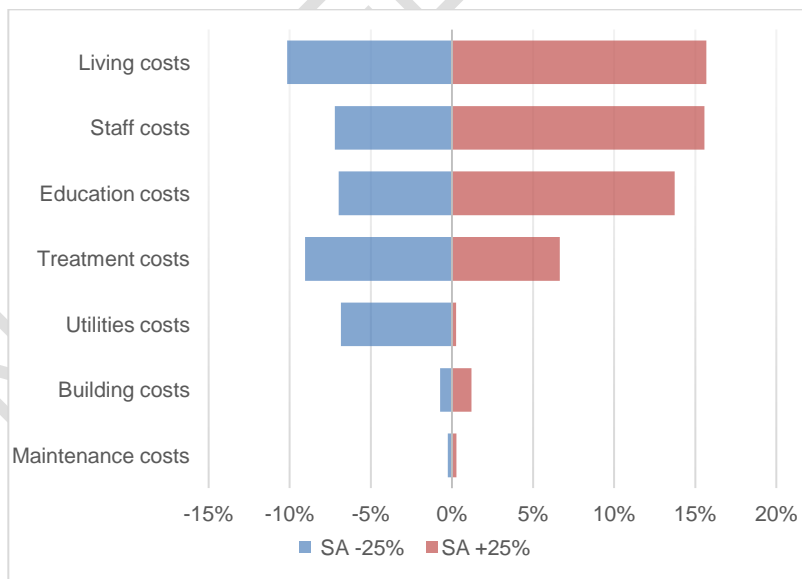


Fig. 1. Univariate Sensitivity Analysis for the average EIP cost (N=238)

3.2. BIVARIATE ANALYSIS

Using Kruskal-Wallis test, these factors are significant (P value $< .05$); children age, annual family income, ASD level, EIP types, EIP frequency and EIP duration. For binomial variables, Mann-Whitney U test was used, and the test showed significant results (P value $< .05$) with these factors; centre-based type, centre-based distance, home relocation and family support. Therefore, the null hypothesis for those factors were rejected.

3.3. MULTIVARIATE ANALYSIS

Multiple linear regression (MLR) was used to identify the predictors for the total annual average costs of EIP. Eight variables were included in the primary model which were family income, ASD level, EIP types, EIP frequency, EIP duration, centre-based type, relocation, and family support. The included variables were chosen at the significance level of *P* value less than 0.25, based on the work by Bendel and Afifi (1977) on linear regression. All variables were categorized into two groups. Reference groups (were labelled as 0) for each significant variable were identified as follows; annual parents' income less than RM100,000, low level of ASD (Level 1 and 2), EIP types (1 type per week), EIP frequency (less than 3 sessions per week), EIP duration (less than 5 hours per week), public EIP centre, parents who not relocated for ASD-related services, and low family support level. They were analyzed using 'ENTER' and 'STEPWISE' methods. Assumptions for multiple linear regression were checked. Partial regression plots for linear relationship was not done in view of categorical data. There was no multicollinearity and no significant outlier. Residual was normally distributed as observed by Q-Q plot of studentized residual. A model generated by 'ENTER' method having the highest adjusted R square and was chosen as the preliminary model.

For the preliminary model, the multiple regression statistically significant predicted average of EIP cost, $F(7,957) = 12.506$, $P = .05$, adj. $R^2 = 0.280$. However, only five were statistically significant to the prediction ($P = .05$), except for EIP duration ($P = .257$), home relocation ($P = .172$) and family support ($P = .099$). The five significant variables were EIP type, EIP frequency, centre-based type, ASD level, and family income. For the final model, the multiple regression model statistically significant predicted average EIP cost, $F(8,001) = 12.506$, $P = 0.05$, adj. $R^2 = 0.270$. The summary of multiple linear regression can be seen in **Table 4**.

The final predictive model was derived as follow: Total annual average costs of EIP = 7799.599 + 6593.020 (family income) + 5688.508 (ASD level) + 3731.508 (EIP type) + 3639.020 (EIP frequency) + 4300.819 (centre-based type).

Table 4. Summary of multiple linear regression (N=238)

Variable	Unstandardized coefficient		Standard coefficient	<i>t</i>	<i>p</i> -value	95% confidence interval (CI)	
	B	SE	B			Lower bound	Upper bound
Constant	7799.599	1258.275		6.199	.001	5320.493	10278.705
Family income	6593.020	1332.215	.283	4.949	.001	3968.234	9217.806
ASD level	5688.508	1668.629	.193	3.409	.001	2400.905	8976.112
EIP type	3731.508	1266.203	.168	2.947	.004	1236.782	6226.234
EIP frequency	3639.020	1062.830	.194	3.424	.001	1544.987	5733.054
Centre type	4300.819	1092.592	.224	3.936	.001	2148.148	6453.491

Inference was made to reference group. Based on the final model, 27% of average EIP cost can be explained by the predictors. Respondents with annual family income of more than RM100,000 are expected to have RM6,593 higher cost than the families with lower annual family income. Respondents having more severe ASD children (Level 3) require RM5,688 higher cost in providing support compared to less severe ASD children (Level 1 and 2). Respondents with ASD children received more than 1 type of EIP per session require RM3,732 higher cost than the counterpart. Respondents with ASD children received 3 and more EIP sessions per week require RM3,639 higher cost than the counterpart. Respondents with ASD children in the private EIP centre-based require RM4,300 higher cost than children in the public EIP centre-based.

In determining the financial burden of families with ASD child, there was a significant difference between household income groups with services rehabilitation ($P = .05$). To improve the health outcome, the families with above average household income groups put a higher commitment to their child's therapy, compared to lower household income group [10]. Among the very low-income group, trade-offs were made between expenditures for the special needs' child and basic living expenses and between care of children and other demands. The complex relationships between disability, poverty, and welfare does expose the families with ASD children at greater risk of experiencing financial hardship [23]. The demands of autism diagnosis and treatment in lower household income group can seriously outstrip the family resources. In US, the annual cost of intervention for ASD child was estimated 3 to 5 times higher among very dependent and semi dependent group of ASD children, compared to normal children [24]. Due to severe restriction in cognitive, social communication and rigidity of behaviour, high ASD level usually require child assistance that able to monitor the child all the time. In UK, cost for ASD child with more severe levels (presence of an intellectual disability) require 2 to 3 times higher cost compared to ASD child without intellectual disability [25], of which greater resources incurred to the families and caregivers for an intensive EIP-related therapy. The largest contributors to total costs in across all age groups were special education, including early intervention services, and indirect costs, such as parental productivity loss. Regarding

347 the programme characteristics, the school services were the biggest contributor to costs associated with childhood ASD
348 ($P = .05$), due to the increased use of special education services [15].
349

350 Other retrieved factors such as intellectual disability and comorbidities were excluded from the present study because
351 different setting and practice were implemented in Malaysia. In terms of severity classification, the level of intelligent
352 quotient (IQ) is not a requirement for ASD children that is diagnosed in Malaysia, compared to the practice from other
353 country, which incorporated the element of IQ in classifying the severity of ASD [26][23][22]. Regarding comorbidities, it
354 was reported by several to have relationship with the ASD-related intervention and management [23][27][15][10].
355 Nonetheless, this factor was also excluded because it is one of the present study's exclusion criteria.
356

357 4. CONCLUSION

358
359 The total annual average costs of EIP, average education costs, average treatment costs, and average living costs per
360 ASD child were estimated at RM15,158; RM3,896; RM1,948; and RM4,409 respectively. There is a relationship between
361 total annual average costs of EIP, and its contributing factors as follows; family income, ASD level, EIP types, EIP
362 frequency, EIP duration, centre-based type, home relocation, and family support. Following the multiple regression
363 analysis, the finding shows that 27% of an average EIP cost can be predicted by the combination of these factors; EIP
364 types, EIP frequency, centre-based type, ASD level and family income.
365

366 COMPETING INTERESTS

367
368 Authors have declared that no competing interests exist.
369

370 CONSENT

371
372 All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication
373 of this case report and accompanying images. A copy of the written consent is available for review by the Editorial
374 office/Chief Editor/Editorial Board members of this journal.
375

376 ETHICAL APPROVAL

377
378 This study was registered under the National Medical Research Register, Ministry of Health, Malaysia (Ref.: NMRR-19-
379 936-45682). The ethical approval to carry out this research was obtained from the Human Ethical Committee of Universiti
380 Putra Malaysia (Ref.: JKEUPM-2019-080). Permission was obtained from the facilities involved in the study [(Ref.:
381 KURNIA.600-8/2/2(10) dated 22 April 2019); (UKM FND/237/2 dated 23 April 2019); approval feedback forms (Lampiran E
382 dated 10 May 2019 and 17 May 2019)]. The consent from respondents (parents) was obtained prior to the data collection.
383

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441

442 **Appendix 1 - Ovid keywords**

443 Question: What are the factors associated with the costs of EIP for children with ASD?

444 Search terms

446

PICO	MeSH Term	Free Text/Text Word
P= children with ASD	Autism Spectrum Disorder	autism spectrum disorder autism spectrum disorders spectrum disorders, autism autism adj1 spectrum disorder*.tw.
	Autistic Disorder	Autism Autism.tw. autism, early infantile early infantile autism infantile autism, early early infantile adj1 autism.tw.

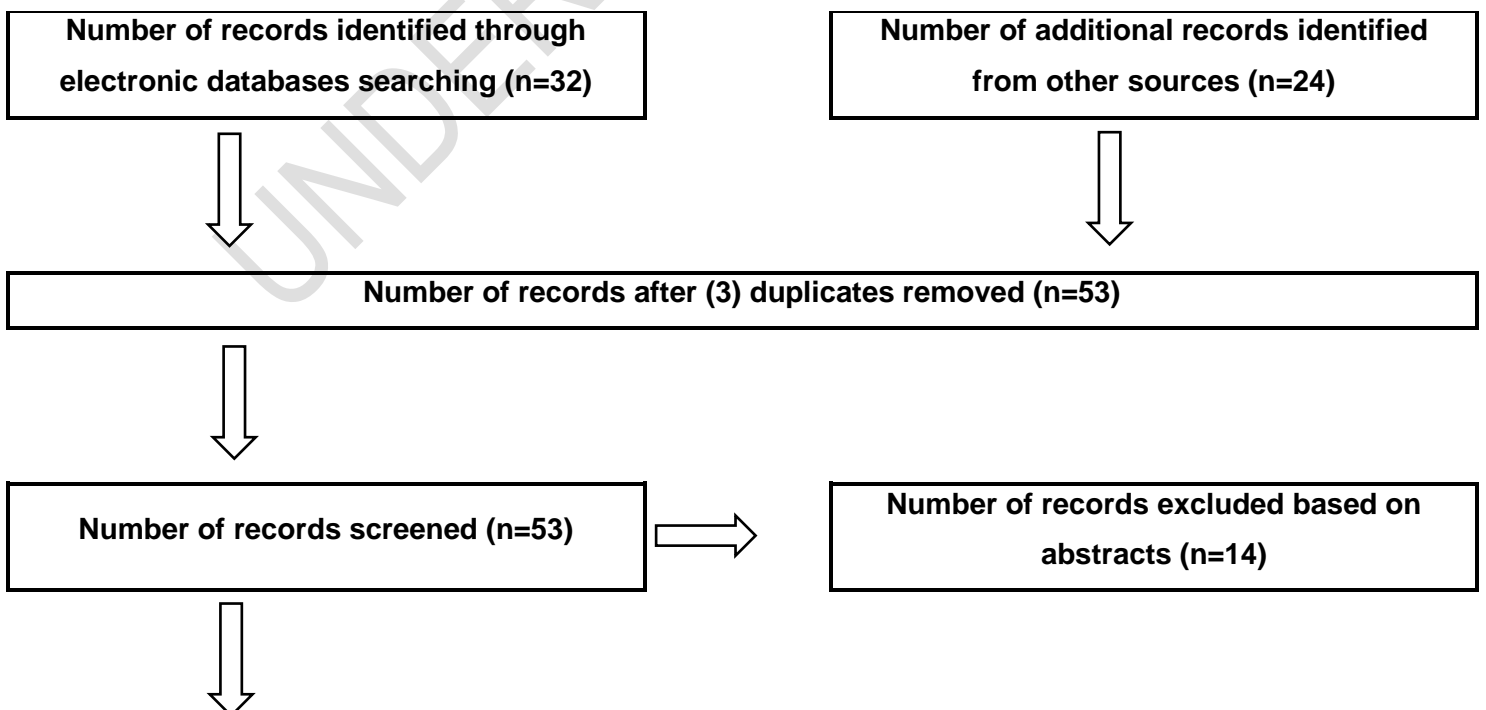
PICO	MeSH Term	Free Text/Text Word
		<p>autism, infantile infantile adj1 autism.tw.</p> <p>autistic disorder disorder, autistic disorders, autistic autistic adj1 disorder*.tw.</p> <p>infantile autism infantile autism.tw.</p> <p>kanner syndrome kanners syndrome kanner* adj1 syndrome.tw.</p> <p>kanner's syndrome kanner's syndrome.tw.</p>
I= early intervention	"Early Intervention (Education)"	<p>early intervention early interventions intervention, early interventions, early early adj1 intervention*.tw.</p> <p>head start program head start program program, head start head start adj1 program*.tw.</p>
	Early Medical Intervention	<p>early medical intervention early medical interventions intervention, early medical interventions, early medical early medical adj1 intervention*.tw.</p> <p>medical intervention, early medical interventions, early early adj1 medical intervention*.tw.</p>
C=		
O= cost analysis	"Costs and Cost Analysis"	<p>analyses, cost analysis, cost cost analyses cost analysis cost adj1 (analyses or analysis).tw.</p> <p>analyses, cost-minimization analysis, cost-minimization cost-minimisation adj1 (analyses or analysis).tw.</p> <p>comparison, cost</p>

PICO	MeSH Term	Free Text/Text Word
		comparisons, cost cost comparison cost comparisons cost adj1 comparison*.tw. cost costs cost*.tw. cost, cost analysis costs, cost analysis cost analysis adj1 cost*.tw. cost measure cost measures measure, cost measures, cost cost adj1 measure*.tw. cost minimization analysis cost-minimization analyses cost-minimization analysis (cost-minimization or cost minimization) adj1 (analyses or analysis).tw. pricing pricing.tw.

447

448 **Appendix 2 – The search process**

449



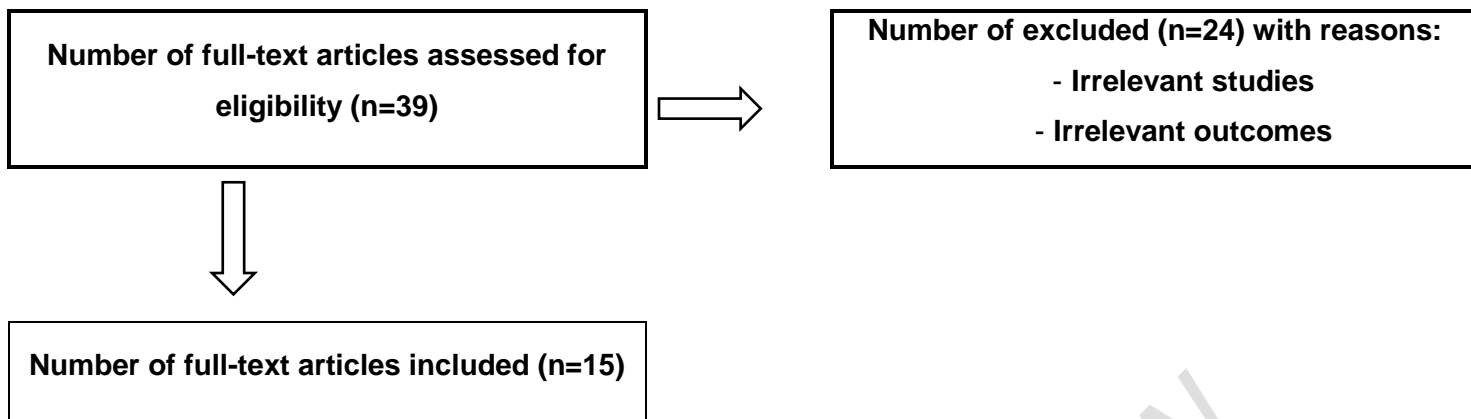


Figure 1 - The search process and flow according to the PRISMA guideline

Appendix 3 – Results of factors contributing to ASD costs

Based on the systematic review on factors associated with ASD-related costs in this study, the results were tabulated in

Table 1.

Table 1 - Summary of factors associated with the cost of ASD-related management and interventions.

N	Study	Outcome	Factors associated				Result/Conclusion
			Sociodemographic	Health services	Environmental	ASD level	
1	Cost Analysis in Early Intervention Escobar et al., 1994, United States, Cross-sectional cost analysis	Average cost of early intervention with children with disabilities including ASD		1. Cent re-based type 2. Program character istics 3. Staff - child ratio 4. EIP centr	1. Family support	1. Severity level 2. Disability level	Based on program characteristics, the range in cost estimates was from \$3,228 to \$14,123 per child annually, by which the centre-based programmes showed higher expenditure compared to the home-

N	Study	Outcome	Factors associated			Result/Conclusion
				e dista nce		based progra mmes. Overall, direct service person nel account ed for the highest percent age of cost.
2	The Economic Impact of Autism in Britain K. Järbrink et al., 2001, Britain, Cross-sectional cost analysis	The economic costs of ASD	1.	S 1. Family support p e c i a l e d u c a t i o n	1. Functioning level	The annual societal cost for the UK was estimated to exceed £1 billion. The lifetime cost for a person with autism exceeded £2.4 million.
3	The Cost-effectiveness of Expanding Intensive Behavioral Intervention to All Autistic Children in Ontario S. Motiwalla et	The costs and consequences of expanding Intensive Behavioral Intervention (IBI)	1. Age	1. Program characteristics 2. Specialty therapy	1. Functioning level	Positive outcomes were demonstrated from expansion of the current intervention program offered by the government

N	Study	Outcome	Factors associated			Result/Conclusion	
4	<p>al., 2006, Canada, Cross-sectional cost-effectiveness analysis</p> <p>The Lifetime Distribution of the Incremental Social Costs of Autism</p> <p>M. Ganz, 2007, United States, Cross-sectional cost analysis</p>	<p>The lifetime per capita incremental societal cost of ASD</p>	<p>1. Age</p>	<p>1. S</p> <p>2. B</p> <p>3. B</p> <p>4. B</p> <p>5. B</p> <p>6. B</p> <p>7. B</p> <p>8. B</p> <p>9. B</p> <p>10. B</p> <p>11. B</p> <p>12. B</p> <p>13. B</p> <p>14. B</p> <p>15. B</p> <p>16. B</p> <p>17. B</p> <p>18. B</p> <p>19. B</p> <p>20. B</p> <p>21. B</p> <p>22. B</p> <p>23. B</p> <p>24. B</p> <p>25. B</p> <p>26. B</p> <p>27. B</p> <p>28. B</p> <p>29. B</p> <p>30. B</p> <p>31. B</p> <p>32. B</p> <p>33. B</p> <p>34. B</p> <p>35. B</p> <p>36. B</p> <p>37. B</p> <p>38. B</p> <p>39. B</p> <p>40. B</p> <p>41. B</p> <p>42. B</p> <p>43. B</p> <p>44. B</p> <p>45. B</p> <p>46. B</p> <p>47. B</p> <p>48. B</p> <p>49. B</p> <p>50. B</p> <p>51. B</p> <p>52. B</p> <p>53. B</p> <p>54. B</p> <p>55. B</p> <p>56. B</p> <p>57. B</p> <p>58. B</p> <p>59. B</p> <p>60. B</p> <p>61. B</p> <p>62. B</p> <p>63. B</p> <p>64. B</p> <p>65. B</p> <p>66. B</p> <p>67. B</p> <p>68. B</p> <p>69. B</p> <p>70. B</p> <p>71. B</p> <p>72. B</p> <p>73. B</p> <p>74. B</p> <p>75. B</p> <p>76. B</p> <p>77. B</p> <p>78. B</p> <p>79. B</p> <p>80. B</p> <p>81. B</p> <p>82. B</p> <p>83. B</p> <p>84. B</p> <p>85. B</p> <p>86. B</p> <p>87. B</p> <p>88. B</p> <p>89. B</p> <p>90. B</p> <p>91. B</p> <p>92. B</p> <p>93. B</p> <p>94. B</p> <p>95. B</p> <p>96. B</p> <p>97. B</p> <p>98. B</p> <p>99. B</p> <p>100. B</p>	<p>1. Childcare</p> <p>2. Home improvement</p> <p>3. Transportation</p>	<p>1. Dependency level</p>	<p>The lifetime per capita incremental societal cost of autism was estimated at \$3.2 million.</p>

N	Study	Outcome	Factors associated				Result/ Conclusion
				a			
				c			
				t			
				e			
				r			
				i			
				s			
				t			
				i			
				c			
				s			
			3.	S			
				p			
				e			
				c			
				i			
				a			
				l			
				t			
				h			
				e			
				r			
				a			
				p			
				y			
6	Cost Comparison of Early Intensive Behavioral Intervention and Special Education for Children with Autism	The costs of special education for ASD	1. Age	1. B	1. Disability level	Total cost-saving following early behavior therapy would save \$2.09 billion to the health care providers.	
				e			
				h			
				a			
				v			
				i			
				o			
				r			
				a			
				l			

N	Study	Outcome	Factors associated	Result/Conclusion
1.	m G. Chas son et al., 2007, Texa s, Cross - sectio nal cost comp ariso n		t h e r a p y	
			2. P r o g r a m	
			i n t e n s i t y	
			3. S t a f f :	
			c h i l	

UNDER PEER REVIEW

N	Study	Outcome	Factors associated				Result/Conclusion
7	Economic Cost of Autism in the UK Knap et al., 2009, United Kingdom, Cross-sectional cost analysis	The economic consequences of ASD	1. Age 2. Residence location	1. Supportive family 2. Care	1. Family support	1. Intellectual disability	Depending on age, the average annual cost per child with ASD without intellectual disability ranged from £1214 to £21,090. With presence of intellectual disability, the lifetime cost of ASD was 50 percent higher compared to ASD without intellectual disability.

N	Study	Outcome	Factors associated	Result/Conclusion	
8	The Economics of Autism in Egypt R. Mendoza, 2010, Egypt, Cross-sectional	The economic costs of ASD	<ol style="list-style-type: none"> 1. Age 2. Household income 3. Educational level 4. Residence location 	<ol style="list-style-type: none"> 1. C 1. Family support 	The home-based program was widely implemented by most Egyptian families with ASD members,

N	Study	Outcome	Factors associated	Result/Conclusion
1	cost analysis		a	compared to the centre-based programmes in most of the developed country
			s	
			e	
			d	
			t	
			y	
			p	
			e	
			2. P	
			r	
			o	
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			t	
			e	
			r	
			i	
			s	
			t	
			i	
			c	
			s	
			3. B	
			e	
			h	
			a	

UNDER PEER REVIEW

N	Study	Outcome	Factors associated	Result/Conclusion
			v i o r t h e r a p y 4. E l P c e n t r e d i s t a n c e	
9	Autism Spectrum Disorders and Health Care Expenditure	The mean expenditure among children with ASD	1. Age	1 The medical expenditure for ASD child is higher with the presence of an

N	Study	Outcome	Factors associated	Result/Conclusion
0	nditur es G. Peac ock et al., 2012, Unite d State s, Cross - sectio nal cost analy sis			intellect ual disabilit y, compar ed to other factors.
1 0	The cost of autis m spect rum disor ders C. Horlin et al., 2014, Austr alia, Cross - sectio nal cost analy sis	The costs of ASD	1. Intellectual disability	The costs needed to support the develo pment of childre n with ASD may have detrime ntal conseq uences for the wellbei ng of the child with ASD and family membe rs, especia lly for low income families

UNDER PEER REVIEW

N	Study	Outcome	Factors associated			Result/Conclusion	
1	Economic Burden of Childhood Autism Spectrum Disorders T. Lavell et al., 2014, United States, Cross-sectional cost analysis	The annual utilization and costs for health care, EIP centre services, ASD-related therapies, family-coordinated services, and caregiver time	1. Special education	2. Cent-re-base-d type		1 In all children with parent-reported ASD, the EIP centre services were the biggest contributor to costs associated with childhood ASD due to the increased use of special education services in this group.	
1	Costs of autism spectrum disorders in the United Kingdom and the United States A. Buescher et al., 2014, United Kingdom & United States, Cross-sectional cost analysis	The costs of ASD	1. Age	1. Special education	1. Child care 2. Family support	1. Intellectual disability	The cost of supporting an individual with an ASD without intellectual disability was \$1.4 million in the United States and £0.92 million (US \$1.4 million) in the United Kingdom. The largest cost components for children were special education services and parental

N	Study	Outcome	Factors associated				Result/Conclusion
13	Comparing service use and costs among adolescents with autism spectrum disorders, special needs and typical development. B. Barrett et al., 2015, United Kingdom, Cross-sectional cost analysis	The services and associated costs for ASD	1. Age	1. Special education	1. Severity level 2. Disability level	In regression analysis, lower age and lower adaptive functioning were associated with higher costs in the groups with an autism spectrum disorder	
14	The economic costs and its predictors for childhood autism spectrum disorders in Ireland: A cross-sectional study	The social cost of childhood ASD and relationship between state and family OOP expense	1. Household income	2. Cent re-base d type 3. Special education	1. Severity level 2. Intellectual disability	The average cost of ASD-related management and interventions per child incurred by the families was estimated at	

N	Study	Outcome	Factors associated				Result/Conclusion
	How is the burden distributed? A. Roddy et al., 2018, Netherlands, Cross-sectional cost analysis	Expenditure					€28,464.89 per year. Families that had a child whose ASD severity was classified as level 2 moderate under DMS-5 criteria were found to have €3100.48 more out-of-pocket expenditure in comparison to families who had a child with level 1 mild ASD
15	The economic burden of families with autism spectrum disorders (ASD) children in Malaysia S. Kamaralzaman et al., 2018, Malaysia, Cross-sectional cost	The economic burden of families with ASD child	1. Age 2. Household income	1. Services rehabilitation special education 2. Special education	1. Domestic helper 2. Transportation	1. Co-morbidities	The average cost incurred by families with ASD children in 2014 is RM36,728.43. There is significant difference between household income groups with services rehabilitation (p = 0.005), and

N	Stud	Outc	Factors associated	Result/
o	y	ome		Conclu
	analy	sis		special educati on (p = 0.001).

462

463 Appendix 4 – Estimation of total annual average costs of EIP

464

465 1. Annual staff emolument

466 **Table 1 - The estimation of annual staff cost utilized for EIP (N=238)**

467

EIP centre	Annual total staff cost ¹ (RM)	Total no. of staff	Total no. of EIP staff	Proportion of EIP staff cost ²	Annual total EIP staff cost ³ (RM)	Annual average EIP staff cost per child (RM)
Centre 1	1,625,000.00	65	54	0.83	1,348,750.00	3,371.88
Centre 2	350,000.00	14	13	0.93	325,500.00	5,425.00
Centre 3	288,000.00	11	10	0.91	262,080.00	4,368.00
Centre 4	374,400.00	14	13	0.93	348,192.00	4,352.40

469 ¹Estimated based on the total number of staffs in respected EIP centre

470 ²Proportion of EIP staff cost = Total no. of EIP staff / Total no. of staff

471 ³Annual EIP staff cost = Total annual staff cost * Proportion of EIP staff cost

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473

474 2. Annual utilities cost

475 **Table 2 - The estimation of annual utilities cost utilized for EIP (N=238)**

476

EIP center	Total floor area (ft ²)	EIP floor area (ft ²)	Annual total utilities cost ¹ (RM)	Proportion of EIP utilities cost ²	Annual total EIP utilities cost ³ (RM)	Annual average EIP utilities cost per child (RM)
Centre 1	113256	22651	271,814.00	0.20	54,362.80	135.91
Centre 2	6400	1600	15,360.00	0.25	3,840.00	64.00
Centre 3	3200	1400	7,680.00	0.44	3,379.20	56.32
Centre 4	5400	1800	12,960.00	0.33	4,276.80	53.46

478 ¹Estimated based on Malaysia utilities data published online at <https://www.numbeo.com/cost-of-living/>; utilities cost per floor area per month in Kuala Lumpur

480 ²Proportion of EIP utilities cost = EIP floor area / Total floor area

481 ³Annual EIP utilities cost = Total annual utilities costs x Proportion of EIP utilities cost

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485

486 3. Annual maintenance cost

487 **Table 3 - The estimation of annual maintenance cost utilized for EIP (N=238)**

488

EIP center	Annual total maintenance cost ¹ (RM)	Total floor area (ft ²)	EIP floor area (ft ²)	Proportion of EIP maintenance cost ²	Annual total EIP maintenance cost ³ (RM)	Annual average EIP maintenance cost per child (RM)
Centre 1	297,297.00	113256	22651	0.20	59,459.40	148.65
Centre 2	16,800.00	6400	1600	0.25	4,200.00	70.00
Centre 3	8,400.00	3200	1400	0.44	3,696.00	61.60
Centre 4	14,175.00	5400	1800	0.33	4,677.75	58.47

¹Estimated based on the floor area (ft2) used for EIP activities in 2018

²Proportion of EIP maintenance cost = EIP floor area / Total floor area

³Annual EIP maintenance cost = Total annual maintenance costs x Proportion of EIP maintenance cost

4. Annual capital cost

Table 4 - The estimation of annual capital cost utilized for EIP (N=238)

EIP center	Total floor area (ft ²)	EIP floor area (ft ²)	Cost ¹ (RM)	Years of completed	Working life (Years)	Useful life (Years)	Annual total building cost ² (RM)	Proportion ³	Annual total EIP building cost ⁴ (RM)	Annual average EIP building cost per child (RM)
Centre 1	113256	22651	27,407,952.00	2015	25	22	1,717,613.09	0.20	343,522.62	858.81
Centre 2	6400	1600	1,548,800.00	2013	25	20	97,060.85	0.25	24,265.21	404.42
Centre 3	3200	1600	358,400.00	2016	25	23	22,460.36	0.50	11,230.18	187.17
Centre 4	5400	1800	604,800.00	1987	25	31	0	0	0	0

¹Construction costs; estimated based on the JUBM & Arcadis Construction Cost Handbook Malaysia 2018, cost per floor area (RM / ft²) at the years of completed

²Annual total building cost = Construction cost / Annualization factors (3% discounting rate, lifespan 25 years)

³Proportion of EIP building cost = EIP floor area / Total floor area

⁴Annual EIP building cost = Annual building cost * Proportion of EIP building cost

NB Other capital costs data such as vehicle, equipment, and furniture were not retrievable

5. Annual patient cost

Table 5 - Annual out-of-pocket (OOP) expenditure reported per family due to having a child with ASD (N=238)

Type of expenses	Proportion*	Centre 1 (RM)	Centre 2(RM)	Centre 3(RM)	Centre 4 (RM)
1. Average education costs:					
1.1. Special education	0.11	532.40	2,024.00	745.25	1,210.00
1.2. Autism friendly activities	0.08	387.20	1,472.00	542.00	880.00
1.3. Childcare and assistance	0.16	774.40	2,944.00	1,084.00	1,760.00
1.4. Training/support costs	0.03	145.20	552.00	203.25	330.00
Sub-total	0.38	1,839.20	6,992.00	2,574.50	4,180.00
2. Average treatment costs:					
2.1. Medical costs	0.19	919.60	3,496.00	1,287.25	2,090.00
Sub-total	0.19	919.60	3,496.00	1,287.25	2,090.00
3. Average living costs:					

3.1. Living costs	0.29	1,403.60	5,336.00	1,964.75	3,190.00
3.2. Travel costs	0.09	435.60	1,656.00	609.75	990.00
3.3. Others	0.05	242.00	920.00	338.75	550.00
Sub-total	0.43	2,081.20	7,912.00	2,913.25	4,730.00
Grand total**	1	4,840.00	18,400.00	6,775.00	11,000.00

*Proportion of total OOP expenditure on EIP-related activities; adapted from Roddy et al., 2014 (N=195)

**Reported by parents of ASD children from 4 different EIP centre in Klang Valley

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