A STUDY OF FACTORS AFFECTING THE OCCURRENCE OF DOWN SYNDROME IN NEGERI SEMBILAN MALAYSIA

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For my beloved Family

Bab, Chelsea, Summy, K.K and Emma

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ABSTRACT

Due to the fact of the high correlation between advanced maternal age and the risk of Down syndrome, genetic and socio- demographic factors of population are expected to have considerable effect on Down syndrome births. The main objective of this research was to assess the effect of genetic and socio-demographic factors within Malaysia in number and incidences of DS. Three hypothesis were tested using 104 DS data and 204 NDS data in Negeri Sembilan, obtained through questionnaire. The hypothesis tested included whether there is a relationship between DS cases and advanced maternal age in Malaysian population, whether there is relationship between genetic factors and DS cases in Malaysian population and lastly whether there is a relationship between DS cases and certain socio-demographic factors in the Malaysian population. Regression analysis having become a standard statistical tool for analysis, probit model, linear probability model and multiple logistic model were used for analysing DS data against genetic and socio-demographic variables while simple logit and probit models were used to analyze DS data against maternal age. For each analysis, these models were compared using Akaike information criteria to determine the model with the best fit for prediction. The results show a significant relationship between maternal age and DS cases. It was also found that DS is not genetic and cannot be transferred from parent to offspring. Race, place of residence and mothers' education level were found to have significant influence on occurrence of DS in Malaysia. Paternal age, Smoking habit, pre-natal scan, and heredity were found to be insignificant factors in the occurrence of DS in Malaysi.

ABSTRAK

Oleh kerana adanya korelasi yang tinggi antara usia ibu yang meningkat dengan risiko sindrom Down, faktor genetik dan sosio-demografi penduduk diharapkan dapat memberi kesan yang besar terhadap kelahiran sindrom Down. Objektif utama penyelidikan ini adalah untuk menilai pengaruh faktor genetik dan sosio-demografi di Malaysia dalam jumlah dan kejadian DS. Tiga hipotesis diuji menggunakan 104 data DS dan 204 data NDS di Negeri Sembilan, yang diperoleh melalui soal selidik. Hipotesis yang diuji merangkumi sama ada terdapat hubungan antara kes DS dan usia ibu yang meningkat pada populasi Malaysia, sama ada terdapat hubungan antara faktor genetik dan kes DS pada populasi Malaysia dan terakhir sama ada terdapat hubungan antara kes DS dan faktor sosio-demografi tertentu dalam penduduk Malaysia.Analisis regresi telah menjadi alat statistik standard untuk analisis, model probit, model kebarangkalian linear dan model logistik berganda digunakan untuk menganalisis data DS terhadap pemboleh ubah genetik dan sosio-demografi sementara model logit dan probit sederhana digunakan untuk menganalisis data DS terhadap usia ibu. Untuk setiap analisis, model ini dibandingkan dengan menggunakan kriteria maklumat Akaike untuk menentukan model dengan ramalan yang paling sesuai. Hasilnya menunjukkan hubungan yang signifikan antara usia ibu dan kes DS. Juga didapati bahawa DS tidak genetik dan tidak dapat dipindahkan dari ibu bapa ke keturunan. Kaum, tempat tinggal dan tahap pendidikan ibu didapati mempunyai pengaruh yang besar terhadap kejadian DS di Malaysia. Umur ibu bapa, kebiasaan merokok, imbasan pra-kelahiran, dan keturunan didapati sebagai faktor yang tidak signifikan dalam kejadian DS di Malaysia.

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LIST OF SYMBOLS AND ABBREVIATIONS

H_0	-	Null hypothesis
H_1	-	Alternative hypothesis
ANOVA	-	Analysis of variance
ASD	-	Autism spectrum disorder
CDC	-	Centre for disease control
CDSS	-	Canadian Down Syndrome Society
CRB	-	Community – based rehabilitation program
DS	-	Down Syndrome
NCBDDD	-	National centre for birth defects and developmental disabilities
NDSS	-	National Down Syndrome Society
NDS	-	No Down Syndrome
OR	-	Odds ratio
PNS	-	Pre - natal scan
PWDs	-	Persons with disability
RM	-	Malaysia Ringgit (Malaysian currency)
SPSS	-	Statistics Software
TPR	-	Total prevalence ratio
WHO	-	World Health Organisation

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LIST OF PUBLICATIONS

1 Opara Otuodi Chigozie, Suliadi Firdaus Sufahani, Kamil Khalid, Azila M. Sudin (2020). A Statistical Study On the Relationship Between Maternal Age and Down Syndrome Birth in Malaysia. *International Journal of Scientific &Technology Research*, 9(3); pp (6677-6680) (published indexed in SCOPUS).

2 Opara Otuodi Chigozie, Suliadi Sufahani, Kamil Khalid Lee Kah Howe (2020). Epidemiological Study of the Influence of Socio -Demographic Factors on the Occurrence of Down Syndrome in Malaysia, *Journal of Physics*, IOP Publishing (Submitted)

CHAPTER 1

INTRODUCTION

This chapter focuses on introduction of the research which includes types and possible causes of Down syndrome (referred to as DS in this study), the antecedent of DS and its evolution was discussed. The research problem was analysed to explore the abnormalities of DS. Statistics facts and rate of DS in Malaysia was discussed. The objectives were outlined in section 1.5, scope of the research was discussed in section 1.6, and the significance of the research was listed in section 1.7.

1.1 General introduction

According to Jones & Smith (2006), DS is caused by an error in cell division resulting in an additional chromosome 21. It is the most commonly diagnosed chromosomal abnormality affecting the individual's mental and physical growth. Each cell in the human body contains a nucleus; which store genetic materials in genes that carry the codes responsible for every inherited trait. These genes are grouped along rod-like structures known as chromosomes. There are 23 pairs of chromosomes in the nucleus of every cell, with half of these chromosomes inherited from each of the parents.

DS occurs when an individual has a complete or partial extra copy of chromosome 21. This extra copy changes the individual's developmental process and gives rise to the occurrence of certain attributes which are associated with DS. DS is referred to as a condition and is physically diagnosed by the manifestation of certain features or characteristics. These features include low muscle tone, round face, slanted eyes, short stocky build (Hayes & Batshaw, 1993; James *et al.*, 1999).

DS is one of the most occurring chromosomal disabilities, about 1 out of every 691 babies are born with the condition each year (Centre for disease control, 2012). DS is diagnosed after birth, by observation of the manifestation of certain physical characteristics. It can also be diagnosed before birth through pre-natal screening and testing. Pre-natal screening assesses the probability of a foetus being abnormal, or already having an abnormality. It does not recognise the existence of DS, but the decision to go for pre-natal diagnostic tests may arise as a result of pre-natal scan. The cause of DS has been linked to a genetic adaptation of chromosome 21 (Sherman *et al.*, 2007) that results in deficiencies in both cognitive and adaptive functioning (Naess *et al.*, 2011; Penna & D'Andre-Penna, 2009). As observed by Eisenhower *et al.* (2005), persons with DS have a bigger risk for experiencing health problems like Obesity (Chad, Jobling & Frail, 1990), heart defects (Vida *et al.*, 2005), Ocular (Stephen *et al.*, 2007) and auditory disorders (Shott *et al.*, 2001) in addition to other disadvantages.

The first full explanation of this situation was done by Dr John Langdon Down in 1866. Dr Down worked as administrator of Earls wood asylum for idiots in Surrey England from 1858 to 1868 and did over time observe and investigate large number of people with mental problems. He recommended an ethnic arrangement of "congenital idiocy" based on appearance and racial pattern (Down, 1866). He suggested in his classification, 5 different varieties; i. Caucasian ii. Malayan iii. Ethiopian iv. American-native v. Mongolian.

Figure 1.1: DS children in Negeri Sembilan.

In his report, Down (1866) noted some of the striking physical presentation (See Figure 1.1) and behavioural peculiarity of persons with DS. He concluded mistakenly that DS was caused by tuberculosis in the parents. His major contribution was his successful differentiating of DS from other cases with similar mental and cerebral disabilities. Due to this pioneer work, the condition became known as DS. The exhaustive DNA arrangement of human chromosome 21 was resolved in 2000, which has changed our perception of DS (Gardiner & Davisson, 2000).

1.2 Background of study

Ever since the discovery of the extra 21st chromosome was made, various researchers have attempted to explore the origin of non-disjunction of chromosome 21. In recent times, there has been progress in the study and diagnosis of DS. Majority of the studies into the causes of human deformity has concentrated on causes from the mother, either before or after fertilization. This attention may have been due to the well-established correlation between birth defects and maternal drug exposures and infections (Lian *et al.*, 1986). Most experimental research work has had to focus on mother/embryo exposures while some little work being done on paternal exposures has yielded little contribution to occurrence of malformation in off springs.

1.2.1 Statistics facts and rates on Down syndrome around the world

According to the World Health Organisation (WHO)**,** 1 out of every 700 babies born in the United States is expected to have DS. The estimated cases of DS are between 1 in 1000 to 1 in 1,100 live births worldwide (WHO, 2018). It is estimated that roughly 3000 to 5000 children are born in the United States each year with this abnormality and there are believed to be about 250,000 families in the United States of America who are afflicted by this syndrome (WHO). Babies of every race have equal chances of having DS (CDSS, 2019). According to the National Down Syndrome Society in the United States, maternal age is the only certain risk factor for DS with mothers who are older than 35 expected to have a baby concerned by the situation, with a 1 in 350 chance of conceiving a child with DS and increasing to 1 in 100 by age 40 and approximately 1 in 30 by age 45.

In a study to analyse recent trends in DS in China on the basis of 1996 to 2011 control data for DS from Chinese birth defects audit, it was seen that total prevalence ratio (TPR) was 3.05 per 10,000 births which was low compared to TPR of 9.07 per 10,000 live births in Turkey before the year 2000 and 9.90 after year 2000 (Acikbas *et al.*, 2012).

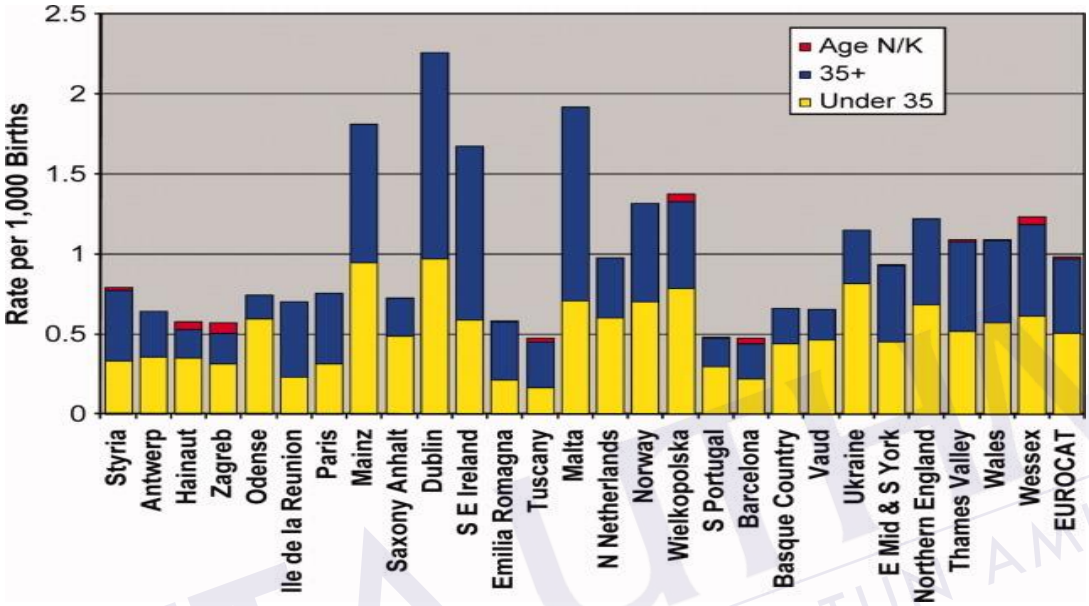

Figure 1.2: Prevalence of DS livebirths per 1000 births for EUROCAT registries. (EUROCAT Guide, 2011).

Figure 1.2 shows the prevalence of DS livebirths per 1000 births for EUROCAT registries, with an overall DS livebirth prevalence of approximately 1 per 1000 with about half of the cases born to women 35 years of age and older.

1.2.2 Statistics facts and rates on Down syndrome in South-East Asia

In a study in three provinces in southern Thailand Jaruratanasirikul *et al.* (2017), aimed at determining the prevalence rate of DS, data collected during the period 2009-2013, showed that of the 186,393 births recorded during the study period, 226 babies were diagnosed with DS, showing a prevalence of 1.21 per 1000 births. This was significantly higher in older mothers, ranging from 0.47 (95% CI 0.25-0.67) in mothers aged < 30 years to 0.88 (95% CI 0.59-1.17) in mothers ≤ 35 years ($p < 0.01$) and to 4.74 (95% CI 3.95 – 5.53) in mothers ≥ 35 years ($p < 0.001$). This shows conclusively that DS prevalence in Southern Thailand significantly increased with

increase in maternal age. In Taiwan, South East Asia, it was observed that there were 0.63 cases of DS per 1000 births before 1994, which further decreased to 0.23 cases per 1000 births between 1994 and 1995 (Jou *et al.*, 2005).

1.2.3 Statistics facts and rates of Down syndrome in Malaysia

In Malaysia like every other country in the world, DS has attracted a lot of attention. In a previous study of occurrence of DS in Malaysia, prevalence of DS was reported to be 1 in 950 live births and it was seen to be more prevalent among the three largest ethnic groups (Malay 1 out of 981 births, Chinese 1 out of 940 births and Indians 1 out of 860 births). This rate of occurrence of DS in Malaysia has been rated as much lower than those from the western population (Hoe *et al.*, 1989). Also, in another study, Boo *et al.* (1989) observed that the incidence of DS among Malaysian live born increased considerably where the maternal age is more than 35 years. In Azman *et al.* (2007), it was found that 64% of DS occurrences correlated with mothers aged 35 years and above. However, all these analyses and studies in Malaysia above, emphasised more on maternal age effect and little or nothing on paternal age effect. Therefore, this study aims at studying the parental age effect and the possible effect of other factors such as parental education level, parental place of residence (rural or urban), parental smoking habit, race and pre-natal scanning on the occurrence of DS in Malaysia.

1.2.4 Jabatan Kebajikan Masyarakat

The Jabatan Kebajikan Masyarakat (JKM) was founded in April 1946 to assist the Malaysian government in achieving national advancement. Since the end of the world war II, it has performed various functions ranging from preventive to rehabilitation of victims of the war and other persons with disabilities (PWDs) and to enhance the community's well-being through professional social welfare services, social development and a strategic sharing of responsibilities.

1.2.4.1 Community recruitment program (Program Pemulihan Dalam Komuniti)

Program Pemulihan Dalam Komuniti (PDK) is a program created by the Department of Disability Development (JPOKU) under the JKM. It is a strategy in the development of local communities for rehabilitation, training, education, equal opportunities and social integration of people with disabilities (OKUs) as can be seen in Figure 1.3 and Figure 1.4.

Figure 1.3: DS students engaged in skills acquisition in PDKs in Negeri Sembilan, Malaysia.

PDKs are implemented through integrated efforts of disabled persons, families, communities and health services, education, vocational and social services. This program is operated throughout the country with the active involvement of the community either at PDK or at home.

1.2.4.2 Role of the Jabatan Kebajikan Masyarakat in this study

The JKM has provided this study with the DS Malaysians through their PDK (see Figure 1.5) facilities where data have been collected for this research. Permission was granted by the JKM headquarters in Putrajaya through the JKM in Negeri Seremban (see Appendix C), whose PDKs were used for this research. Any other information or data related to DS in Negeri Sembilan has been accessed through the JKM.

PDK in Seremban

PDK in Port-Dickson

PDK in Mantin

PDK in Pekan Rembau

Figure 1.4: Some PDKs in Negeri Sembilan.

1.3 Problem statement

Various studies around the world have proven that advanced maternal age is a certain risk factor for DS. Advanced maternal age has also remained the only well-documented risk factor of maternal meiotic non-disjunction (Azman *et al.*, 2007). According to America's Essential Hospitals, a large and growing body of evidence shows that socio-demographic factors can influence health outcomes. In addition, demographic factors such as geographic region, maternal education, marital status and ethnicity have been observed to affect DS in the United States (Parker *et al.*, 2010;

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