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Research Paper

" Assessing the Parental Origin and Predisposing Risk Factors of Trisomy 21: An Analytical Study of Environmental and Familial Influences "

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Abstract
Background*: Down Syndrome (DS) or Trisomy 21 continued being the most common form of chromosomal anomaly. While advanced age of maternal was known as one of the risk factors, the role of paternal in this condition and other possible factors such as environmental, lifestyle, and familial have not been adequately studied among North African countries.* ***Objective*** *: To determine the parental involvement and predisposing risk factors in the development of Down Syndrome in children through studying environmental, lifestyle and familial factors among affected families in Al-Bayda city, Libya.* ***Methods****: A descriptive cross-sectional analytical research design was adopted which involved 456 participants (152 children suffering from DS and their biological parents). A set of multi-dimensional questionnaire was distributed to the subjects for collecting information about demographic characteristics, parents' health conditions, environmental factors, reproductive history, and consanguine marriages. Statistical analysis of the data collected was done using IBM SPSS software applying descriptive and inferential statistic (chi square test), at significance level less than 0.05.* ***Results****: It was found that increased maternal age (≥35 years) was highly significant in relation to the occurrence of DS ($\chi^2 = 14.82$, $p = 0.001$). Significant relationships existed between DS and paternal exposure to various risk factors such as smoking (62.5% of fathers), radiation exposure (23.7%), and chemicals/pesticides (18.4%). In addition, consanguineous marriages were prevalent among 38.2% of parents. Maternal hormonal problems (28.9%), folic acid deficiency (41.4%), and a history of miscarriages (34.2%) were significantly related to DS. Interestingly, increased paternal age (≥40 years) had a significant association ($\chi^2 = 8.67$, $p = 0.013$).* ***Conclusion****: DS is considered a multifactorial disease with various contributing risk factors from both the mother and father, as well as exposure to certain environmental risks and genetic predispositions in the family line. The importance of paternal risk factors in the development of DS needs to be investigated further.*

Keywords: *Down syndrome, Trisomy 21, Parental risk factors, Environmental influences, Consanguinity*

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I. Introduction

Down Syndrome (DS), caused mainly by Trisomy 21, is the most frequent chromosomal abnormality in the *world*. In clinical terms, DS is caused by a cellular defect called non-disjunction that causes an extra copy of chromosome 21. Even though advanced maternal age is a risk factor already recognized since ancient times, modern genetics has become aware of other factors involved in these diseases **(Antonarakis et al., 2020).** Despite the predominance of maternal nondisjunction events in trisomy 21 etiology, molecular genetic research employing DNA polymorphism markers has established that around 5% to 10% of the cases originate from the father **(Rana et al., 2025).** In recent years, it has been pointed out that advanced paternal age and certain environmental factors may impact the quality of spermatogenesis, which could lead to the generation of aneuploid sperm **(Lahimer et al., 2023).**

Several epidemiological studies have started to emphasize the importance of paternal involvement in DS etiology. One study based on a population of more than 2 million births in Shenzhen, China, found a U-shaped

relationship between paternal age and the risk of trisomy 21, whereby there was a significantly increased likelihood of trisomy 21 in men below 20 years of age (AOR = 2.40) and men above 40 years old (AOR = 1.44), after adjusting for maternal age and other covariates **(Zhou et al., 2024).**

The germline of the parent is very susceptible to the influence of external agents. Ionizing radiation and chemical toxicity have been established as the major cause of oxidative stress that could cause problems in the meiosis process during the creation of the gamete **(Aitken., 2020).** In addition, other risk factors like the smoking habits of an individual, and the excessive use of technology (electromagnetic fields), have been considered in recent studies for possible inducers of epigenetic modifications and DNA damage in the mother and father **(Vlachou et al., 2025, Lamzouri et al., 2025).**

Folic acid metabolism is essential when it comes to proper DNA methylation and chromosomal stability. This pathway has been suggested to possibly malfunction because of nutritional problems that can lead to Down syndrome in maternal **(Zargar et al., 2025).** Another major consideration in chromosomal non-disjunction is a person's family history. These include any history of thyroid disease and consanguinity **(Ray et al., 2018).**

In a recent study conducted in Libya**, Al-Nagar et al. (2026)** highlighted the following factors as major contributing causes: increased parity, high BMI of parents, and low folic acid consumption by the mother. Although our knowledge about the causality of Down syndrome is becoming more sophisticated, studies conducted regarding the association between multiple risk factors in the Libyan context have so far remained few. The available studies in Libya have mainly centered around the cytological diagnosis of the disease and estimating its frequency, while paying little attention to environmental and familial determinants that could potentially explain the presence of the disorder. Nonetheless, the role of paternal factors, such as occupation exposures and lifestyle habits, remains poorly understood. It is against this background that the present study aims at bridging this gap by undertaking an extensive analysis into the origin and predisposing risk factors of Down syndrome in Al-Bayda city of Libya.

II. Materials and Methods

This research used a descriptive , analytical and cross-sectional design in order to examine various risk factors among parents and environmental issues that may be related to Down syndrome. This research was carried out at specialized centers for the development of mental abilities and special education institutions situated in Al-Bayda City, Libya. These institutes were selected due to the fact that they created an appropriate environment for obtaining information regarding the condition. The time duration of the research ranged from January 1, 2025 to April 30, 2025. In total, the sample included 456 people, out of which there were 152 children suffering from Down syndrome and their parents (152 mothers and 152 fathers). The selection criteria for this study necessitated the presence of a confirmed diagnosis of Down Syndrome among the selected children and also included having the availability of both the parents who would contribute towards the history. The main tool used in gathering information was a questionnaire that covered both the genetic, environmental, and lifestyle factors associated with Down Syndrome. Data was collected using interviews and filling of the questionnaires by the selected families at the institutions designated for carrying out this research activity. All the families involved in the study were given a briefing on the purpose of the research. The ethical considerations were adhered to by upholding the voluntary status of involvement in the study. The informed consent of all parents was sought, and confidentiality ensured as a way of safeguarding the anonymity of both parents and the children. After completion of the data collection process, the data collected was then coded and analyzed using a statistical analysis tool known as SPSS. Descriptive statistics were obtained in the form of frequencies and percentages. The inferential statistics used to analyze the relationships between the parental risks factors and the incidence of Down Syndrome included the use of chi-square tests. The level of significance used in the analysis of data was 0.05.

III. Results

A total of 152 families was used for the study; each family consisted of a child diagnosed with Down syndrome, their mother, and father, giving a total of 456 respondents. The findings for all descriptive and inferential statistical analyses performed in various areas including demographics, health, environment, reproduction, and family are detailed below. Table 1 gives an account of the sociodemographic profile of the study subjects. A large proportion of the mothers were aged above 35 years, 44.1%. Of the total number of mothers, 27.6% were between the ages of 35 and 39 years while 16.4% were aged ≥40 years. In the case of the fathers, almost two-thirds (57.2%) were of 35 years or above in age, with 28.3% being aged ≥40 years. With regards to BMI, the category of overweight/obese was dominant among both the groups, with 60.5% of mothers and 65.1% of fathers falling into that category.The common blood group of mothers and fathers was O. Results of parents' health status and medical history are described in Table 2. Thyroid abnormalities were observed much more frequently among mothers (21.1%) than fathers (7.2%) ($\chi^2 = 12.45$, $p = 0.001$). Hormonal abnormalities were

identified in 28.9% of mothers and 10.5% of fathers ($\chi^2 = 16.23$, $p < 0.001$). Chronic diseases occurred in 31.6% of mothers and 19.1% of fathers ($\chi^2 = 6.42$, $p = 0.011$). Pre-conception use of medications was observed in 34.9% of mothers and 14.5% of fathers ($\chi^2 = 17.08$, $p < 0.001$). The use of hormonal and fertility drugs was identified in 23.7% of mothers. No significant difference was found regarding epilepsy ($p = 0.539$). Table 3 shows the distribution of environmental and lifestyle factors.

The prevalence rate of tobacco smoking was significantly higher among fathers (62.5%) compared to passive smoking among mothers (3.9%) (χ^2=118.76; p<0.001). The exposure to radiation (X-rays) was observed in 12.5% mothers and 23.7% fathers (χ^2=6.54; p=0.011). Exposure to Chemicals or pesticides occurred in 5.9% mothers and 18.4% fathers (χ^2=11.32; p=0.001). Use of mobile phones constantly was very common in both mothers (84.2%) and fathers (91.4%). However, the difference between two groups failed to achieve statistical significance (p=0.060). The reproductive and maternal health-related factors are outlined in Table 4. The deficiency of folate or vitamins was observed among 41.4% of mothers and was associated significantly with DS ($\chi^2 = 14.56$, $p < 0.001$). The history of miscarriage occurred among 34.2% of participants ($\chi^2 = 9.87$, $p = 0.002$). The poor mental condition during the pregnancy was found for 44.7% of mothers ($\chi^2 = 11.34$, $p = 0.001$). Complications during the pregnancy occurred in 30.9% of cases ($\chi^2 = 7.63$, $p = 0.006$). Irregular periods (25.7%), loss of appetite during the pregnancy (28.9%), infections of viruses or bacteria during the pregnancy (17.8%), and contraception usage (27.0%) also associated. The information regarding family history and consanguinity is presented in Table 5. In 38.2% of families, consanguinity was found to be significantly associated with DS (χ^2= 12.78; $p < 0.001$). The family history of DS existed in 15.1% of families (χ^2= 8.94; $p = 0.003$). Also, the family history of any other genetic disorder was evident in 27.0% of families (χ^2= 7.56, $p = 0.006$). Table 6 shows the relationship between parental age and DS. Advanced maternal age (≥35 years) was seen among 44.1% of participants and significantly associated with DS ($\chi^2 = 14.82$, $p = 0.001$). Likewise, advanced paternal age (≥40 years), observed among 28.3% of fathers, was also significantly associated with DS ($\chi^2 = 8.67$, $p = 0.013$), highlighting the importance of the role of paternal age in DS incidence. The features of the 152 children with DS have been presented in Table 7. Most of the children with DS were males (57.9%). The majority of DS cases had a natural mode of delivery (64.5%) and 35.5% were delivered through cesarean delivery. Prematurity among children with DS is seen in 22.4%, while oxygen deficiency during birth is found in 19.1% of cases. Heart disease, which is one of the common complications of DS, was observed among 44.1% of patients.

Table 1: Demographic Profile of Parents (N = 152 Families)

Variable	Category	Mothers n (%)	Fathers n (%)
Age at child's birth	<25 years	18 (11.8)	8 (5.3)
Age at child's birth	25–29 years	29 (19.1)	22 (14.5)
Age at child's birth	30–34 years	38 (25.0)	35 (23.0)
Age at child's birth	35–39 years	42 (27.6)	44 (28.9)
Age at child's birth	≥40 years	25 (16.4)	43 (28.3)
BMI Classification	Underweight (<18.5)	8 (5.3)	5 (3.3)
BMI Classification	Normal (18.5–24.9)	52 (34.2)	48 (31.6)
BMI Classification	Overweight (25–29.9)	56 (36.8)	62 (40.8)
BMI Classification	Obese (≥30)	36 (23.7)	37 (24.3)
Blood Type	A	38 (25.0)	42 (27.6)

Blood Type	B	35 (23.0)	33 (21.7)
Blood Type	AB	22 (14.5)	18 (11.8)
Blood Type	O	57 (37.5)	59 (38.8)

Table 2: Parent's Health & Medical Conditions (N = 152)

Health Factor	Mothers n (%)	Fathers n (%)	χ^2	p-value
Thyroid disorders	32 (21.1)	11 (7.2)	12.45	**0.001***
Hormonal problems	44 (28.9)	16 (10.5)	16.23	**<0.001***
Epilepsy	7 (4.6)	5 (3.3)	0.38	0.539
Chronic diseases	48 (31.6)	29 (19.1)	6.42	**0.011***
Use of hormonal/fertility drugs	36 (23.7)	—	—	—
Pre-pregnancy medication use	53 (34.9)	22 (14.5)	17.08	**<0.001***

*Statistically significant at $p < 0.05$

Table 3: Environmental & Lifestyle Exposure (N = 152)

Exposure Factor	Mothers n (%)	Fathers n (%)	χ^2	p-value
Tobacco smoking	6 (3.9) passive smoking	95 (62.5)	118.76	**<0.001***
Radiation exposure (X-ray)	19 (12.5)	36 (23.7)	6.54	**0.011***
Chemical/pesticide exposure	9 (5.9)	28 (18.4)	11.32	**0.001***
Constant mobile phone use	128 (84.2)	139 (91.4)	3.54	0.060

*Statistically significant at $p < 0.05$

Table 4: Reproductive & Maternal Health Factors (N = 152 Mothers)

Factor	n (%)	χ^2	p-value
History of miscarriage	52 (34.2)	9.87	**0.002***
Pregnancy complications	47 (30.9)	7.63	**0.006***
Folate/vitamin deficiency	63 (41.4)	14.56	**<0.001***

Loss of appetite during pregnancy	44 (28.9)	5.21	**0.022***
Irregular menstrual cycle	39 (25.7)	4.88	**0.027***
Viral/bacterial infection during pregnancy	27 (17.8)	6.12	**0.013***
Poor psychological state	68 (44.7)	11.34	**0.001***
Use of contraceptives	41 (27.0)	3.92	**0.048***

*Statistically significant at $p < 0.05$

Table 5: Family History and Consanguinity (N = 152 Families)

Factor	n (%)	χ^2	p-value
Consanguineous marriage	58 (38.2)	12.78	**<0.001***
Family history of DS	23 (15.1)	8.94	**0.003***
Family history of genetic disorders	41 (27.0)	7.56	**0.006***

**Statistically significant at $p < 0.05$*

Table 6: Relationship between Parent's Age and Down Syndrome (N = 152)

Variable	Category	n (%)	χ^2	p-value
Maternal age	<35 years	85 (55.9)	14.82	**0.001***
Maternal age	≥35 years	67 (44.1)	—	—
Paternal age	<40 years	109 (71.7)	8.67	**0.013***
Paternal age	≥40 years	43 (28.3)	—	—

**Statistically significant at $p < 0.05$*

Table 7: Child Profile (N = 152)

Characteristic	Category	n (%)
Gender	Male	88 (57.9)
Gender	Female	64 (42.1)
Type of birth	Natural	98 (64.5)

Type of birth	Cesarean	54 (35.5)
Premature birth	Yes	34 (22.4)
Premature birth	No	118 (77.6)
Oxygen deficiency at birth	Yes	29 (19.1)
Oxygen deficiency at birth	No	123 (80.9)
Congenital heart disease	Yes	67 (44.1)
Congenital heart disease	No	85 (55.9)

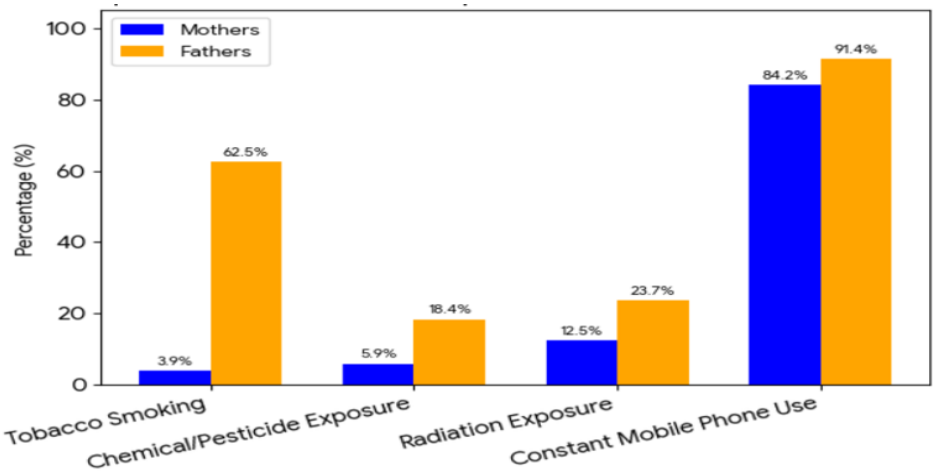

Figure 1: Comparative Environmental Exposures Between Mothers and Fathers

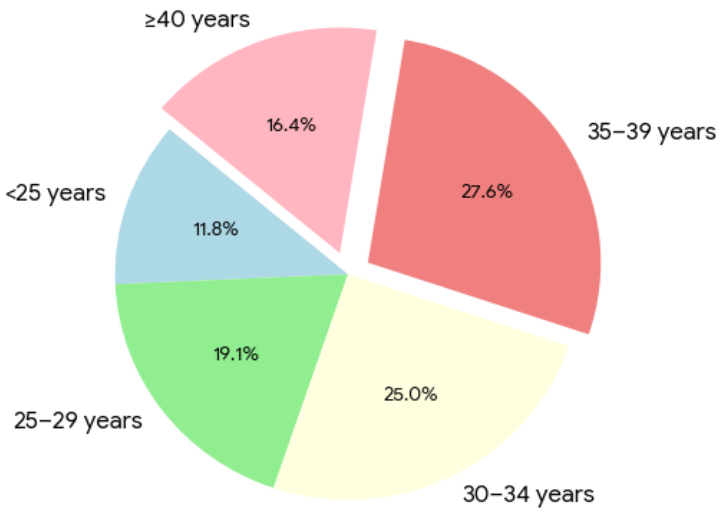

Figure 2: Distribution of Maternal Age Groups (Highlighting ≥35 years at 44.0%)

IV. Discussion

The results from the study have provided sufficient evidence to support the multi-factorial causality of Down Syndrome, emphasizing the known factor of maternal age, alongside highlighting the underrated paternal and environmental influences. As noted by **Ghosh et al., (2011) and Aprigio et al., (2023),** the occurrence of trisomy 21 increases exponentially in direct relation to increased maternal age, thus corroborating the fact that 44.1% of the women giving birth were above 35 years old. The age-dependent susceptibility is mechanistically related to progressive degeneration of cohesin complexes that cause improper chromosome segregation due to long-term arrest of meiosis in oocytes **(Herbert et al., 2015).**

One of the interesting results in the current research was a statistically significant connection between father's age of ≥40 years and the development of DS with the frequency of 28.3%. The result of this study is consistent with recent findings from a nationwide population study in China indicating that there is a U-shaped relationship between age at paternal and risk for trisomy 21 with odds ratios of 1.44 in fathers aged ≥40 years **(Zhou et al., 2024).** Despite the fact that more than 93% of trisomy 21 occur because of maternal meiotic non-disjunction, 5-10% of cases are caused by paternal chromosomal segregation errors **(Vraneković et al., 2012).**

The high incidence of paternal smoking (62.5%) along with its strong correlation with DS is in line with findings from earlier studies reporting that tobacco use is a risk factor for oxidative stress, DNA damage, and meiotic spindle apparatus dysfunction. As shown by **Ghosh et al. (2011),** periconceptional smoking interacts strongly with nondisjunction genetic risk factors, while smokeless tobacco is linked to shortened maternal telomere length and a threefold greater DS risk **(Ray et al., 2016).**

Likewise, the strong correlations noted with paternal exposure to ionizing radiation (23.7%) and chemical or pesticide exposure (18.4%) are consistent with findings indicating that ionizing radiation, including X-rays used for diagnosis, is known to have a potential to cause chromosomal breakage and disrupt patterns essential for normal chromosome segregation **(Verger, 1997).** Chemical exposure is another facet of environmental hazards. Exposure to chemicals, pesticides, heavy metals, and endocrine disruptors like Bisphenol A (BPA) has been shown to affect epigenetics modifications by altering DNA methylation, leading to possible chromosomal instability during gamete formation **(Rana et al., 2025).**

The prevalence of consanguineous marriages (38.2%) identified in this study has significance in relation to the Libyan population and aligns well with results obtained among other populations from North Africa and the Middle East. Consanguinity leads to a higher chance of being homozygous for recessive genes that may hinder the process of DNA repair or cause nondisjunction **(El-Attar et al., 2019).** The strong correlation between consanguinity and the occurrence of DS cases ($p < 0.001$) observed in this study shows that endogamous marriages represent another level of genetic vulnerability among the studied population.

Folate deficiency found in 41.4% of the mothers has proved to be a strong predictor in this case. This conclusion correlates with the research of **Patterson (2008)**, which showed that folate plays an important role in the process of methylation and that a lack of this substance can result in chromosome 21 hypomethylation and subsequent nondisjunction. Similarly, the study conducted in Libya by Al-Nagar et al. (2026) found that inadequate intake of folic acid by the mother was another major risk factor associated with DS. These studies indicate that DS can no longer be regarded merely as a disease related to age of the mother but rather as a multifactorial disease that is affected by various factors, including genetic and environmental factors of both parents.

V. Conclusions

The results of this study have shown that DS occurrence among Libyans from the Al-Bayda region is associated not only with advanced maternal age but also with the presence of several interacting risk factors including:

1 - Advanced maternal age (≥35 years), which is statistically significant in 44.1% of cases.

2- Several paternally related factors such as smoking (62.5%), radiation (23.7%), chemical exposure (18.4%), and advanced paternal age (≥ 40 years) in 28.3% of participants who had children with DS.

3- Environmental factors that can be considered as modifiable, namely, tobacco smoke and ionizing radiation that affect parents.

4- Consanguineous marriage (38.2%), which is an essential risk factor that requires genetic counseling.

5- Nutritional insufficiencies, especially of folic acid (41.4%), as well as reproductive complications are important risk factors which can be prevented.

6- The father's contribution in the development of DS is an important risk factor that occurs less frequently than the female's but remains statistically significant.

The above results point to the importance of introducing appropriate health programs during pregnancy covering all risk factors of maternal and paternal, genetic counseling programs, and public health initiatives for the Libyan community.

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