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The Pegasus Review: UCF Undergraduate Research Journal

Volume 15 | Issue 1 Article 1

February 2022

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Neda Hamood
University of Central Florida, nhamood@knights.ucf.edu

Vol. 14.2: 1-20

URJ

THE PEGASUS REVIEW:
UNIVERSITY OF CENTRAL FLORIDA
UNDERGRADUATE RESEARCH JOURNAL

Published
February 13th, 2023

Paternal Ages and Genetic Diseases and Congenital Anomalies

By: Needa Hamood
Faculty Mentor: Dr. Raheleh Ahangari
UCF Burnett School of Biomedical Sciences

ABSTRACT: The purpose of this research is to investigate the link between Advanced Paternal Ages (APA) (i.e., APA ≥ 35 years and APA ≥ 50 years) and genetic diseases and congenital anomalies. Currently, the relationship between both APA and genetic diseases and congenital anomalies remains unclear. There is room for improvement, however, to investigate systematically the relationship between specific congenital anomalies in newborns and APA. More recently, the link between APA (as opposed to existing studies analyzing Advanced Maternal Age alone) and genetic diseases has been recognized by researchers, epidemiologists, and various health experts. Thus, this study serves to examine the effect of APA on the likelihood of birth defects using a new dataset intended to discover those relationships. I created three datasets and utilized 12 statistical models to analyze the relationship between Advanced Paternal Ages (APA ≥ 35 years and APA ≥ 50 years, while including Advanced Maternal Age (AMA) [AMA ≥ 35 years]) and reproductive defects. This study focuses on Down syndrome, cleft lip with or without cleft palate, and meningocele/spina bifida, and explores the relationship between both advanced parental ages. I performed the analyses using logistic regression models that provide explanations of the relationship between each birth defect and APA. The results suggest that APA are positively associated with Down syndrome, whereas APA is negatively associated with cleft lip with or without cleft palate.

KEYWORDS: Advanced Paternal Age, Advanced Maternal Age, Genetic Diseases, Congenital Anomalies, Genetics, Down Syndrome, Cleft Lip, Spina Bifida

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INTRODUCTION

In some parts of the world, many hold the view that a woman's suitable childbearing age is around ten years younger than men.[1] The so-called "gender gap in marital timing,"[2] or biological clock, may be influenced by societal taboos and myths surrounding fertility that attribute reproductive defects solely to the mother's age.[3] Medical studies have linked high-risk pregnancies among aging mothers (Advanced Maternal Age ≥ 35 years) to an aged reproductive system and body[4] (Lampinen et al., 2009). Consequently, many studies focus on the connection between Advanced Maternal Age (AMA) and genetic diseases. These studies support the theory concerning aging female fertility and reproductive abnormalities.[5] However, the recorded AMA only accounts for about half of reproductive anomalies.[6] Thus, potential cases of reproductive anomalies concern the same question as this thesis, whether Advanced Paternal Ages (APA ≥ 35 years and APA ≥ 50 years) and AMA contribute to cases of newborns with genetic diseases and congenital anomalies.

Some studies suggest that AMA may be linked with higher prevalence of chronic medical anomalies[7] (Lampinen et al., 2009; Carolan and Nelson, 2007). The links between APA and genetic diseases are becoming increasingly topical among researchers, epidemiologists,[8] and various health experts. This research contributes to further development by investigating whether both paternal and maternal ages increase specific infant anomalies. Moreover, I focus on the effect of APA on the likelihood of birth defects like genetic diseases and congenital anomalies.

Birth defects may manifest either at birth or later in the effected individual's life and could be genetic. Among other predictors, a genetic abnormality in the cell's genetic information (from either one or both parents) can cause mutations from the onset of human reproduction (Kalumuck, 2014).[9] In 1912, Weinberg[10] suggested that if a study could more directly analyze the link between mutations and last-born children, we may better understand susceptibility to dwarfism (or achondroplasia).[11] Haldane (1947) first studied Weinberg's (1912) observation, and suggested that male mutation levels are approximately ten times higher than female mutations. Despite uncertain valuations, this observation was substantiated in incidences of Haemophilia A[12] (a genetic deficit usually impacting males) and Hemophilia B[13] (a genetic bleeding disorder).[14] By advancing Weinberg's (1912) initial theory on genetic mutations we may further our understanding of other genetic diseases regulated by biological functions.

Based on Haldane's (1947) study, Penrose (1955) further studied the genetic mutations model, suggesting that paternal age could be the sole cause of Weinberg's 1912 study (Crow, 2000, p. 40). APA and genetic mutation are possibly linked and might heighten the risk of birth defects. Accordingly, Penrose developed and proposed[15] the 1955 "copy error theory."[16] The higher rate of germ cell division or spermatogenesis in APA relative to the female germ line (or oogenesis) in AMA may be associated with congenital anomalies.[17] In males, the time of spermatogenesis is between 72 - 74 days, which involves division of germ cells during the meiosis and mitosis phases, increasing the vulnerability of "cytotoxic damage" or altering the "DNA[18] sequence" resulting in genetic mutations (Ibid., 2008, p. 30). By the time a male is 35 years, the spermatozoa (or motile sperm cells) will have undergone about "540 divisions and replications" that accumulate in the older father's sperm, thus increasing the likelihood of congenital malformations (Grewal et al., 2012, p. 389). This study uses APA ≥ 35 years as the advanced paternal reproductive age based on the literature analyzing the link between paternal age and genetic abnormalities. Vogel and Motulsky (1997) add that males undergo 840 spermatic replications by age 50, potentially increasing the likelihood of transcription errors throughout the replication process (Penrose, 1955). Thus, considering a higher rate of spontaneous mutations in older sperm, I argue that APA ≥ 35 years and APA ≥ 50 years combined with AMA ≥ 35 years may place a higher probability of birth defects in the couple's newborn. Building on Penrose's (1955) theory, epidemiologists have identified over four thousand "gene disorders" that are inherited, and such chromosomal abnormalities may be identified as numerical[19] and/or structural[20] (Powell-Hamilton, 2018). While science has advanced the classification and categorization of chromosomal abnormalities, there may be further developments on the studies on the link between APA and genetic mutations. Despite the existing theory used to justify the possible connections between disorders in newborns and paternal age, studies remain unsystematic in comparing the APA and AMA on the effect of genetic diseases.

While some findings[21] offer guidance concerning the APA as a potential factor affecting birth defects in newborns, there are some discrepancies that are not accounted for in the analyses (i.e., the female partner's

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age, a larger sample, and observations using reliable sources). Hence, it is difficult to fully analyze the predictors of birth defects that manifest at birth when considering only one parent's age characteristics. Thus, including both advanced parents' ages may provide some explanation in the empirical study of APA and reproductive anomalies.

Since the previous studies use Penrose's (1955) copy error theory to analyze the link between APA and reproductive anomalies, I argue that when APAs are in place, the higher rate of spontaneous mutations may increase the likelihood of birth defects when including the theory on AMA in the analyses.

According to the CDC Natality Registry report, genetic diseases that become apparent or detected at birth are known as congenital anomalies (2020). Thus, this research aims to take a more nuanced approach by identifying genetic diseases that manifest into congenital anomalies in newborns using the CDC Natality Registry[22] (2020) to analyze the link between APA and reproductive anomalies. I focus on genetic birth abnormalities[23] classified under chromosomal[24] abnormalities (Down syndrome) and multifactorial birth defects (cleft lip with or without cleft palate, and meningocele/spina bifida[25]). I argue that congenital anomalies have been traced to genetic mutation using the copy error mechanism to explain the manifestation of genetic birth abnormalities[26] or genetic diseases.

LITERATURE REVIEW

The literature considers that both parents' family history relates to some reproductive anomalies, but there is limited literature that analyzes the relationship of APA, while accounting for AMA, on genetic abnormalities.[27] While extensive studies suggest AMA raises the likelihood of congenital anomalies, very few consider the effect of APA on various congenital anomalies.[28] Additionally, studies that have evaluated APA on congenital anomalies contain few observations and often focus on "APA and Down syndrome," while neglecting other dominant mutations at birth (McIntosh et al., 1995). More recently, though, there have been a few discussions suggesting a connection between APA and "neonatal and pediatric disorders" but there remains a lack of quantitative analyses on this observation.[29] Therefore, we recognize the necessity of including both paternal ages to properly understand the implications of the APAs during reproduction.

Down Syndrome

Down syndrome[30] (identified as Trisomy 21) is more likely to occur from females than males but there is lack of sufficient evidence to exclude males in the causation of this disease (Hassold et al., 1996). Thus, it is reasonable to include paternal age in more clearly determining possible relationships between advanced age and chromosomal abnormalities[31] in newborns.

According to Thompson (2019), it is imperative to ascertain the exposures that yield non-disjunction in oocyte development, which is overwhelmingly age-related, and non-disjunction in sperm development, whereby the paternal age effect is still ambiguous[32].

Cleft Lip

Research suggests a greater emphasis on paternal age as opposed to maternal age in cases related to autosomal dominant congenital diseases (e.g., cleft lip and palate)[33] (Conti and Eisenberg, 2016). To ascertain this phenomenon, Vogel and Rathenberg (1975) and Drost and Lee (1995) explain a difference in gametogenesis[34] between genders (Conti and Eisenberg, 2016). Females are born with all oocytes (i.e., immature egg/ovum) (Gurevich, 2020); consequently, "cell divisions [in females] are completed before birth, [and] there is no increases [in DNA replication] with postnatal age" (Crow, 2000:41). This phenomenon of DNA replication in females, researchers propose, yields a lower likelihood of genetic mutations during the human reproduction stage.

However, spermatogenesis in males is continuous throughout one's age, thus "[increasing] the number of chromosome replication events."[35] The continuous DNA replication processes may produce higher proclivities for copy error mutations, which places a potential causal relationship between paternal aging and genetic diseases (Conti and Eisenberg, 2016).

Spina Bifida

The literal meaning of spina bifida is "cleft spine," and this disease is described by the partial growth of the spine, brain, and/or the layer shielding the spine and brain (Ibid., 2020). Experts believe spina bifida may be caused by multiple factors such as genetic, environmental, and nutritional agents (Ibid., 2020). Additionally, recent studies using birth data suggest that the likelihood of neural tube defects (NTDs[36]) in newborns such as spina bifida may be linked to AMA (Vieira and

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Castillo Taucher, 2005). Studies including paternal age on incidence of spina bifida are scarce although this condition is a genetic disorder. Thus, this study fills the gap in the literature pertaining to the link between APA and genetic diseases and congenital anomalies.

Hypotheses

By applying the copy error theory (Penrose, 1955) to the APA-genetic diseases relationship, this study offers clarification on how APAs may affect the likelihood of three separate genetic diseases in newborns. This approach considers three hypotheses that empirically test (using models A, B, C, and D) the relationship between paternal ages and genetic diseases:

A Advanced reproductive aging in both the father (paternal age 35+) and mother (maternal age 35+) are more likely to have a newborn with (1) Down syndrome, (2) cleft lip with or without cleft palate, and (3) spina bifida than both parents with non-advanced reproductive aging.

B The interaction between the advanced reproductive aging in both the father (paternal age 35+) and mother (maternal age 35+) are more likely to have a newborn with (1) Down syndrome, (2) cleft lip with or without cleft palate, and (3) spina bifida than both parents with non-advanced reproductive aging.

C Advanced reproductive aging in both the father (paternal age 50+) and mother (maternal age 35+) are more likely to have a newborn with (1) Down syndrome, (2) cleft lip with or without cleft palate, and (3) spina bifida than both parents with non-advanced reproductive aging.

D The interaction between the advanced reproductive aging in both the father (paternal age 50+) and mother (maternal age 35+) are more likely to have a newborn with (1) Down syndrome, (2) cleft lip with or without cleft palate, and (3) spina bifida than both parents with non-advanced reproductive aging.

METHODS

This study on the link between APA and genetic diseases consisting of congenital anomalies was extended to observe individuals with Down Syndrome, those born with a cleft lip (with or without a cleft palate), and spina bifida. These observations were pulled from the CDC Natality Registry database (CDC, 2020) database that systematically compiles reported live births in the U.S., which are provided by CDC Wonder (2020). The CDC Natality Registry database (2020) that consists of the United States Births Vital Statistics[37] from 2016-2019 was used to create these three datasets. All missing or unreported data was eliminated from the overall number of observations in each model and all variables in this research were categorized as dichotomous. In the Down Syndrome model, the number of observations were 3,295,210 (Table 2), the Cleft Lip with or without Cleft Palate model had 3,296,177 observations (Table 4), and the Spina Bifida model had 3,296,177 observations (Table 6).

Dependent Variables

Three dependent variables were used to test the studies' hypotheses, specifically I include genetic diseases that manifest into three different congenital anomalies: Down syndrome, cleft lip (with or without cleft palate), and spina bifida. All dependent variables in this study are dichotomous, whereby the non-confirmed congenital anomaly is coded as "0" and the confirmed congenital anomaly is coded as "1". A separate logistic regression[38] model is used to test the relationship between APA and each congenital anomaly.

Main Independent Variables

The models[39] in this study include the following main independent variables:[40]

1. Advanced Paternal Age[41] [APA ≥ 35 years]
2. Advanced Maternal Age [AMA ≥ 35 years]
3. Advanced Parental Ages[42] (Interaction Effect of APA and AMA [APA ≥ 35 years * AMA ≥ 35 years])
4. Advanced Paternal Age[43] [APA ≥ 50 years]
5. Advanced Parental Ages (Interaction Effect of APA and AMA [APA ≥ 50 years * AMA ≥ 35 years])

Control Variables

The CDC Wonder (2020) database includes various maternal factor types in addition to nutritional, health, lifestyle, and pregnancy complications, which may influence the birth outcome. I use two multifactorial influences: tobacco use during pregnancy and gestational diabetes (CDC, 2020). All models include these two control variables to determine the propensity of Down syndrome, cleft lip (with or without cleft palate), and spina bifida. In this analyses, Table 1 includes the 12 models.

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Table 1. Models to be Analyzed

		Down Syndrome[44]				Cleft Lip (w or w/o Palate)[45]				Spina Bifida[46]			
	Model #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Independent Variables	Advanced Paternal Age 1 (35+)	✔	✔			✔	✔			✔	✔		
	Advanced Maternal Age 35+	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
	Interaction term of Advanced Paternal Ages (APA ≥ 35 years * AMA ≥ 35 Years)		✔				✔				✔		
	Advanced Paternal Age 2 (50+)			✔	✔			✔	✔			✔	✔
	Interaction term of Advanced Paternal Ages (APA ≥ 50 years * AMA ≥ 35 Years)				✔				✔				✔
Control Variables	Tobacco Use	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
	Gestational Diabetes	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Data Analysis

According to this study, the three dependent variables Down syndrome, cleft lip with or without cleft palate, and spina bifida are all binary (0, 1). I used logistic regression to perform three separate analyses and describe the results of the analyses in the next section. The Summary Statistics found in Appendix A show the comparison of two groups[47] (e.g., Down syndrome and APA 35+) to measure the causal relationship.

RESULTS

Down Syndrome and Paternal Ages

This study tested the link between APA and Down syndrome using varying combinations of APA and AMA. Table 2 reports the results of my analyses for each relationship. In Table 2, Models 1 - 4 report the odds ratios derived from each logistic regression analysis.

Hypothesis 1 and Analysis

Model I. The effects of both advanced parental ages are consistent with my expectations and are statistically significant. Hassold et al. (1996) and Thompson (2019) suggested that scientific studies need to include the APA in the potential causation of Down syndrome since the lack of evidence on this relationship is unclear. My findings suggest a 38% increased likelihood of a father age 35+ to have a confirmed Down syndrome case in his newborn. This research offers some promising information to further investigate the link between APA and Down syndrome[48].

Model II. The coefficient of the interaction variable yielded an opposite effect than predicted and is not statistically significant. However, the APA as a separate variable in Model II is significant and suggests a 43% more likelihood of having a newborn with Down syndrome among fathers aged 35+.

Model III. The effects of paternal age 50+ and maternal age 35+ on Down Syndrome are statistically significant. The APA ≥ 50 years is significant as it suggests a 60% increased likelihood of having a newborn with Down syndrome among fathers aged 50+.

Model IV. The interaction effect of both APAs here are not consistent with the expectations defined at the outset of the research and are not statistically significant. But in this model, only the maternal age 35+ proved consistent with the study's expectations, and are thus statistically significant.

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Table 2. Relationship between Down Syndrome and Advanced Paternal Ages

	Dependent variable: Down Syndrome			
	All Advanced Paternal Ages			
	(I)	(II)	(III)	(IV)
Advanced Paternal Age 35+	1.382*** (0.126)	1.433*** (0.176)		
Advanced Maternal Age 35+	4.594*** (0.416)	4.818*** (0.672)	5.487*** (0.397)	5.499*** (0.401)
Advanced Parental Ages 35+		0.923 (0.167)		
Advanced Paternal Age 50+			1.599*** (0.283)	1.791 (0.901)
Advanced Parental Ages Father 50+, Mother 35+				0.880 (0.473)
Tobacco Use	1.258 (0.207)	1.256 (0.207)	1.236 0.203	2.714 (1.388)
Gestational Diabetes	1.307** (0.144)	1.306** (0.144)	1.312 (0.145)	0.470** (0.237)
Constant	0.000*** (7.010)	0.000*** (7.390)	0.000*** (6.920)	0.000*** (6.950)
Observations	3,295,210	3,295,210	3,295,210	3,295,210
Likelihood Ratio	**595.85*** **	**596.04*** **	**589.39*** **	**589.44*** **
Pseudo-R2	0.040	0.040	0.039	0.039

*Notes: Values in parentheses are Standard Error (SE); *p<0.1; **p<0.05; ***p<0.01*

Table 3. Predicted Probabilities of Down Syndrome

Main Independent Variables	***Model***			
	I	**II**	**III**	**IV**
Paternal Age ≥ 35 years = 0	0.0005***	0.0050***		
Paternal Age ≥ 35 years = 1	0.0004***	0.0004***		
Paternal Age ≥ 50 years = 0			0.0005***	0.0005***
Paternal Age ≥ 50 years = 1			0.0006***	0.0005***

*Confidence Level Notes: *p<0.1; **p<0.05; ***p<0.01*

Down Syndrome and Control Variables

In the four models of Table 2, tobacco use during pregnancy was statistically insignificant and concludes no effect on Down syndrome in newborns. However, gestational diabetes is consistent with the expectations of this study and proved statistically significant in all four models. Table 3 displays the predicted probabilities[49] of the models that produced statistically significant results:

Cleft Lip (with or without Cleft Palate) and Paternal Ages

The link between APAs and Cleft Lip with or without Cleft Palate was tested by using varying combinations of APAs and AMA. Table 4 displays the findings of the conducted analyses for each relationship. In Table 4, Models 5 - 8 report the odds ratios derived from each logistic regression analysis.

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Table 4. Relationship between Cleft Lip with or without Cleft Palate and Advanced Paternal Ages

	Dependent variable: Cleft Lip with or without Cleft Palate			
	All Advanced Paternal Ages			
	(V)	(VI)	(VII)	(VIII)
Advanced Paternal Age 35+	0.847**	0.851**		
	(0.055)	(0.062)		
Advanced Maternal Age 35+	0.970	0.987	0.869**	0.868**
	(0.075)	(0.134)	(0.058)	(0.059)
Advanced Paternal Age 35+		0.974		
		(0.161)		
Advanced Paternal Age 50+			0.190	1.152
			(0.247)	(0.366)
Advanced Paternal Ages Father 50+, Mother 35+				1.058
				(0.444)
Tobacco Use	1.504***	1.503***	1.503***	1.503***
	(0.149)	(.0149)	(.0149)	(.0149)
Gestational Diabetes	1.218**	1.218**	1.209**	1.209**
	(0.111)	(0.111)	(0.110)	(0.110)
Constant	0.000***	0.000***	0.000***	0.000***
	(0.000)	(0.000)	(0.000)	(0.000)
Observations	3,296,177	3,296,177	3,296,177	3,296,177
Likelihood Ratio	30.16***	30.19***	24.20***	24.22***
Pseudo-R2	0.001	0.001	0.001	0.001

*Notes: Values in parentheses are Standard Error (SE); *p<0.1**; **p<0.05; ***p<0.01*

Hypothesis 2 and Analysis

Model V. The conducted research concludes a negative effect of paternal age 35+, which was statistically significant, on cleft lip with or without cleft palate. This finding is consistent with the results found in the studies conducted by McIntosh et al. (1995) and Kazaura et al. (2004) where they suggest that younger fathers have a higher likelihood of having newborns with neural tube defects like cleft lip. The findings of this study suggests that fathers over 35 are about 15% less likely to have a child with cleft lip than fathers who are under 35 years of age. Since cleft lip has multifactorial influences, it is reasonable to argue that younger fathers (below 35 years) are more likely to be exposed to environmental and nutritional agents, for example, that may negatively interact with inherent genetic mutations leading to birth defects (Lobo and Zhaurova, 2008). There was no support found that indicate maternal age 35+ increasing the likelihood of cleft lip.

Model VI. There was no support that the interaction of both advance paternal ages (APA ≥ 35 years * AMA ≥ 35 years) increases the likelihood of cleft lip. But like Model V, there was a statistical significance and a negative relationship between cleft lip and APA ≥ 35 years, suggesting a 15% less likelihood of cleft lip in newborns whose father's age is 35+ years. Moreover, this study found no support that maternal age 35+ increases the likelihood of cleft lip.

Model VII. While there was no relationship between cleft lip and paternal age 50+, there was a negative relationship between cleft lip with or without cleft palate and maternal age 35+ with statistically significant results. Essentially, the findings suggest that mothers 35+ years and older have a 14% less likelihood to have a child with cleft lip than mothers who are younger than 35 years of age.

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Model VIII. The interaction effect of both advanced parental ages in Model VIII are not consistent with the study's expectations and are not statistically significant. However, there was a negative relationship between cleft lip with or without cleft palate and maternal age 35+ with statistically significant results. The findings in this model suggest that mothers 35+ years and older have a 14% less likelihood to have a child with cleft lip than mothers who are below the age of 35 years.

Cleft Lip with or without Cleft Palate and Control Variables

In all four models in Table 4, tobacco use during pregnancy and gestational diabetes are consistent with the study's expectations and are statistically significant. The findings in all four models suggest that tobacco use during pregnancy and gestational diabetes increase the likelihood of cleft lip with or without cleft palate in newborns. Table 5 displays the predicted probabilities of the models that produced statistically significant results.

Spina Bifida and Advanced Paternal Ages

This study tested the relationship between APA and Spina Bifida while employing different dimensions of the father's advanced age. Table 6 displays the findings of the analyses for the relationship between spina bifida and (a) APA ≥ 35 years and AMA ≥ 35 years; (b) APA ≥ 35 years and AMA ≥ 35 years, and the interaction between APA ≥ 35 years * AMA ≥ 35 years; (c) APA ≥ 50 years and AMA ≥ 35 years; and (d) APA ≥ 50 years and AMA ≥ 35 years, and the interaction between APA ≥ 50 years * AMA ≥ 35 years.

Hypothesis 3 and Analysis

Model IX. APA has a negative effect but is not statistically significant, whereas AMA has a positive effect on spina bifida but is not statistically significant. Although spina bifida is classified as a genetic birth abnormality, this birth defect manifests from the interaction of genetic mutations and environmental (or multifactorial) influences (Lobo and Zhaurova, 2008). There are numerous multifactorial influences that become confounding variables in this type of genetic disease. Some examples of multifactorial influences include the combination of each parent's environment, daily diet, nutritional deficiencies, maternal infections, consumption of alcohol, drugs, and/or tobacco use, etc. (Berkow et al., 1997). Thus, it is difficult to identify a causal relationship for genetic diseases that have multifactorial influences.

Model X. Like Model IX, Model X yielded similar findings that do not support the hypotheses. Thus, including the interaction variable is not significant for the relationship between spina bifida and the explanatory variable (i.e., APA [APA ≥ 35 years]).

Model XI. Advanced reproductive aging in both father (APA 50+) and mother (AMA 35+) are more likely to have a newborn with spina bifida than both parents with non-advanced reproductive aging. These explanatory variables do not affect the probability of spina bifida and do not reflect statistical significance.

Model XII. The interaction variable of paternal age 50+ and maternal age 35+ does not affect the probability of spina bifida and does not reflect statistical significance.

Table 5. Predicted Probabilities of Cleft Lip with or without Cleft Palate

Main Independent Variables	***Model***			
	V	**VI**	**VII**	**VIII**
Paternal Age ≥ 35 years = 0	0.0002***	0.0002***		
Paternal Age ≥ 35 years = 1	0.0028***	0.0003***		
Paternal Age ≥ 50 years = 0			0.0002***	0.0002***
Paternal Age ≥ 50 years = 1			0.0004***	0.0004***

*Confidence Level Notes: *p<0.1; **p<0.05; ***p<0.01*

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Table 6. Relationship between Spina Bifida and Advanced Paternal Ages.

	Dependent variable: Spina Bifida			
	All Advanced Paternal Ages			
	(IX)	(X)	(XI)	(XII)
Advanced Paternal Age 35+	0.882 (0.106)	0.819 (0.114)		
Advanced Maternal Age 35+	1.165 (0.159)	0.912 (0.242)	1.086 (0.126)	1.074 (0.126)
Advanced Paternal Age 35+		1.424 (0.446)		
Advanced Paternal Age 50+			0.766 (0.346)	0.410 (0.411)
Advanced Paternal Ages Father 50+, Mother 35+				2.400 (2.698)
Tobacco Use	1.423* (0.269)	1.429* (0.270)	1.427* 0.270	1.429* (0.270)
Gestational Diabetes	1.515*** (0.232)	1.518*** (0.233)	1.508*** 0.231	1.508*** (0.231)
Constant	0.000*** (7.930)	0.000*** (8.180)	0.000*** (7.280)	0.000*** (7.300)
Observations	3,296,177	3,296,177	3,296,177	3,296,177
Likelihood Ratio	11.37**	12.71**	10.630**	11.340**
Pseudo-R2	0.001	0.001	0.001	0.001

*Notes: Values in parentheses are Standard Error (SE); *p<0.1; **p<0.05; ***p<0.01*

Spina Bifida and Control Variables

In all four models presented in Table 6, tobacco use during pregnancy and gestational diabetes are consistent with the expectation that tobacco usage increases the likelihood of spina bifida in newborns and are statistically significant. The combination of genetic and environmental agents suggests that spina bifida has multifactorial influences as supported by this study (Conti and Eisenberg, 2016). Tobacco use during pregnancy and gestational diabetes are confounding variables that may influence the reproduction stage, resulting in the birth defect.

DISCUSSION

Limited studies have investigated the link between APA and genetic disease and congenital anomalies systematically (Thompson, 2019). The extent of the study on the relationship between advanced age and reproductive anomalies rely mainly on AMA, while the possible link between APA and reproductive anomalies has been recently reviewed (Halvaei et al., 2020). Thus, this thesis conducts a study to analyze the link between APA and genetic diseases and congenital anomalies to shed light on the topic. In order to fully appreciate whether APA may contribute to birth defects in infants, this study's findings confirm a positive relationship between APA and Down syndrome. Fathers 35+ and 50+ are associated with a higher likelihood of having a newborn with Down syndrome. Essentially, these findings suggest an elevation in the risk for APA and the manifestation of Down syndrome. Considering these outcomes, future studies may analyze these predictions by including more recent observations (from 2020 forward) to reinforce the scientific relationship between APA and Down syndrome.

Interestingly, findings confirm a negative relationship between APA ≥ 35 years and cleft lip with or without cleft palate, which suggests that a father who is younger

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Table 7. Predicted Probabilities of Spina Bifida

Main Independent Variables	***Model***			
	IX	X	XI	XII
Paternal Age ≥ 35 years = 0	0.0001***	0.0001***		
Paternal Age ≥ 35 years = 1	0.0001***	0.0001***		
Paternal Age ≥ 50 years = 0			0.0001***	0.0001***
Paternal Age ≥ 50 years = 1			0.0001**	0.0001

*Confidence Level Notes: *p<0.1; **p<0.05; ***p<0.01*

than age 35 years has a higher likelihood of having a newborn with cleft lip with or without cleft palate. These results are consistent with McIntosh et al. (1995) and Kazaura et al. (2004) who suggest a negative effect of APA and NTDs such as cleft lip. Additionally, this study finds no support for the relationship between APA and spina bifida. This discrepancy could partially be explained by how cleft lip and spina bifida are birth defects that have multifactorial causes, which are not genetic in nature. While there was no causal relationship between Down syndrome and the two control variables (tobacco use during pregnancy and gestational diabetes), this study found a positive relationship between these control variables and cleft lip and spina bifida

CONCLUSION

This study contributes to the literature of reproductive anomalies according to paternal age by analyzing the effects of APA on genetic diseases and congenital anomalies. The results of this study suggest a causal relationship between APA and Down syndrome, but finds no support for the relationship between APA, cleft lip, and spina bifida. Moreover, this study furthers Penrose's (1955) copy error theory by closely examining the father's age relative to birth defects by stating that from age 35 and older, the father sees an increased likelihood of having a newborn with genetic diseases and congenital anomalies. Considering the positive relationship found between Down syndrome, APA, and the negative relationship between cleft lip and APA, this study could be helpful to epidemiology and genetics. The implications in the results may motivate scholars to develop models by incorporating added confounding variables (for instance, socio-economic factors or the paternal diet—including alcohol and/or drug consumption). By including more confounding variables, we may further our understanding of how paternal age affects the likelihood of reproductive anomalies. This study's empirical findings will be useful to future research on paternal age and reproductive health.

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APPENDIX: SUMMARY STATISTICS

Down Syndrome

Down Syndrome	Father ≥ 35 years				Father ≥ 50 years			
	No		Yes		No		Yes	
No	2,223,877	99.99%	1,070,525	99.95%	3,250,496	99.98%	43,906	99.92%
Yes	313	0.01%	495	0.05%	774	0.02%	34	0.08%
Total	**2,224,190**	**100%**	**1,071,020**	**100%**	**3,251,270**	**100%**	**43,940**	**100%**
N=3,295,210	Pr=0.000				Pr=0.000			

Down Syndrome	Mother ≥ 35 years				Both Parental Ages ≥ 35 years			
	No		Yes		No		Yes	
No	2,647,487	99.99%	646,915	99.93%	2,760,605	99.99%	533,797	99.92%
Yes	339	0.01%	694	0.07%	404	0.01%	404	0.08%
Total	**2,647,826**	**100%**	**2,647,826**	**100%**	**2,761,009**	**100%**	**534,201**	**100%**
N=3,295,210	Pr=0.000				Pr=0.000			

Down Syndrome	Father ≥ 50 years * Mother≥ 35 years			
	No		Yes	
No	3,267,729	99.98%	26,673	99.89%
Yes	778	0.02%	30	0.11%
Total	3,268,507	100%	26,703	100%
N=3,295,210	Pr=0.000			

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Cleft Lip

Cleft Lip	Father ≥ 35 years					Father ≥ 50 years				
	No		Yes			No		Yes		
No	2,223,524	99.95%	1,071,077	99.96%		3,250,642	99.95%	43,959	99.95%	
Yes	1,123	0.05%	453	0.04%		1,552	0.05%	24	0.05%	
Total	2,224,647	100%	1,071,530	100%		3,252,194	100%	43,983	100%	
N=3,296,177	Pr= 0.001					Pr= 0.514				

Cleft Lip	Mother ≥ 35 years					Both Parental Ages ≥ 35 years				
	No		Yes			No		Yes		
No	2,647,013	99.95%	647,588	99.96%		2,760,218	99.95%	534,383	99.06%	
Yes	1,298	0.05%	278	0.04%		1,355	0.05%	221	0.04%	
Total	2,648,311	100%	647,866	100%		2,761,573	100%	534,604	100%	
N=3,296,177	Pr= 0.044					Pr= 0.018				

Cleft Lip	Father ≥ 50 years * Mother≥ 35 years				
	No		Yes		
No	3,267,870	99.95%	26,731	99.95%	
Yes	1,562	0.05%	14	0.05%	
Total	3,269,432	100%	26,745	100%	
N=3,296,177	Pr= 0.733				

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Spina Bifida

Spina Bifida	Father ≥ 35 years				Father ≥ 50 years			
	No		Yes		No		Yes	
No	2,224,333	99.99%	1,071,385	99.99%	3,251,740	99.99%	43,978	99.99%
Yes	314	0.01%	145	0.01%	454	0.01%	5	0.01%
Total	**2,224,647**	**100%**	**1,071,530**	**100%**	**3,252,194**	**100%**	**43,983**	**100%**
N=3,296,177	Pr= 0.675				Pr= 0.647			

Spina Bifida	Mother ≥ 35 years				Both Parental Ages ≥ 35 years			
	No		Yes		No		Yes	
No	2,647,949	99.99%	647,769	99.99%	2,761,196	99.99%	534,522	99.98%
Yes	362	0.01%	97	0.01%	377	0.01%	82	0.02%
Total	**2,648,311**	**100%**	**647,866**	**100%**	**2,761,573**	**100%**	**534,604**	**100%**
N=3,296,177	Pr= 0.426				Pr= 0.339			

Spina Bifida	Father ≥ 50 years * Mother≥ 35 years			
	No		Yes	
No	3,268,977	99.99%	26,741	99.99%
Yes	455	0.01%	4	0.01%
Total	**3,269,432**	**100%**	**26,745**	**100%**
N=3,296,177	Pr= 0.886			

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ENDNOTES

1 Allendorf et al., 2017.

2 On average, the suitable age range for a woman to marry is 20 to 25, whereas the man's acceptable age range is between 23 and 30 (Ibid., 2017).

3 Ibid., 2017.

4 As the mother ages, the integrity of the ova deteriorates, which may be linked to both decreased fertility and higher risk of chromosomal abnormalities (Heffner, 2021).

5 Ibid., 2021.

6 Cnattingius et al., 1992; Bianco et al., 1996; Dollberg et al., 1996; Breart et al., 1997; Jolly et al., 2000; Hollier et al., 2000; Reefhuis et al., 2004.

7 Essentially, the literature often studies the relationship between female age and birth anomalies in newborn children, and the alternate relationship between the male's advanced age on reproductive abnormalities remains scarce and unclear (Conti and Eisenberg, 2016).

8 Epidemiologists practice the field of medicine that focuses on the "incidence, distribution, and possible control of diseases and other factors relating to health" (Lexico, 2020).

9 Kalumuck, 2014.

10 Weinberg's (1912) achondroplasia trait observation established the initial conception of human genetics (Crow and Hardy, 1999).

11 Crow, 2000: 40.

12 Becker et al., 1996.

13 Ketterling et al., 1999. Green et al., 1999.

14 Crow, 2000: 40.

15 Penrose (1955) claimed that since male germ cells experience constant mitotic divisions, there may be a higher likelihood of spontaneous mutations in the male germ line than that of the female (Grewal et al., 2012: 387).

16 Grewal et al., 2012.

17 Materna-Kiryluk et al., 2008.

18 DNA is the abbreviation for Deoxyribonucleic acid, which is a molecule that consists of the biological directions that exclusively define the characteristics of each breed (National Human Genome Research Institute, 2020).

19 Structural abnormalities contain anomalies whereby an entire chromosome (or parts of chromosomes) do(es) not properly connect with other chromosomes (i.e., Translocations) and deletions and duplications of several chromosomal parts (Powell-Hamilton, 2018).

20 Thompson, 2019.

21 According to Grewal et al. (2012), some studies analyzed and suggested a positive relationship between APA and heart defects in newborns (Lian et al., 1986; Olshan et al., 1994; Yang et al., 2007; and Materna-Kiryluk et al., 2008), neural tube and upper limb defects (McIntosh et al., 1995), orofacial clefts (Materna-Kiryluk et al., 2008; McIntosh et al., 1995; Polednak, 1976; and Bille et al., 2005) and malformations in the nervous system (Kazaura et al., 2004). Conversely, similar studies found a negative relationship suggesting there is a higher likelihood of "congenital heart defects" among young paternal age (Zhan et al., 1995), "neural tube defects" (McIntosh et al., 1995; Kazaura et al., 2004), "anencephaly and spina bifida" (Yang et al., 2007; Kazaura et al., 2004), and "gastroschisis" (Yang et al., 2007; Materna-Kiryluk et al., 2008; and Archer et al., 2007). However, these studies are inconsistent in using reliable sources to obtain data on birth defects, do not include the partner's age in their analyses (i.e., the mother's age), and obtain limited sample size of birth defects in their analyses (Grewal et al., 2012).

22 Collection of data for all variables used in this research are obtained with full permission from: United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention" "(CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics, Natality public-use data 2016-2019, on CDC" WONDER Online Database, October 2020. Accessed at http://wonder.cdc.gov/natality-expanded-current.html on Jun 6, 2021, 1:24:47 PM;" United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention" "(CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics, Natality public-use data 2016-2019, on CDC" "WONDER Online Database, October 2020. Accessed at http://wonder.cdc.gov/natality-expanded-current.html on Jun

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23 Down syndrome results from a chromosomal abnormality alone, whereas cleft lip and spina bifida may manifest from the interaction of genetic mutations and environmental effects leading to multifactorial influences (Lobo and Zhaurova, 2008).

24 Chromosomal diseases have been linked to a complex interaction of one's composition and—in some cases—environmental influencers.

25 Spina Bifida is Meningocele, which is characterized with "a sac fluid [that] comes through an opening in the baby's back" (CDC, 2020). In this research, I will use "spina bifida" when discussing this reproductive anomaly.

26 While it is not considered the only mechanism behind congenital anomalies in newborns, the copy error theory proposes that numerous "cell divisions during spermatogenesis allow for the introduction of transcription errors" throughout the replication process, which are later transmitted as "gene mutations" (Penrose, 1955: 312-313).

27 Powell-Hamilton, 2018.

28 McIntosh et al., 1995.

29 Thompson, 2019: 2; Andersen and Urhoj, 2017; Sigman, 2017.

30 According to the Global Down Syndrome Foundation (Children's Hospital of Philadelphia, 2020), the precise cause of the disease remains ambiguous, but research suggests that Down syndrome "increases with maternal age", especially after a female is 35-years or older (Lobo and Zhaurova, 2008).

31 During the non-disjunction process—when the chromosomes fail to separate properly—Down syndrome develops when three copies of chromosome exist rather than two (Dreamscape, 2020). In confirmed Down syndrome cases, non-disjunction occurs in "anaphase, when a pair of homologous chromosomes do not separate before being distributed into two daughter cells," which results in cells where "one cell has two copies of a chromosome," while the other cell does not have any copies (Sparkes and Crandall, 1972).

32 Thus, based on Penrose's (1955) theory, which suggests that gene expression may also stem from the [aging] male, incorporating the father's age in epidemiological and/or genetic studies "may provide leads to causal factors" to various types of genetic disorders (Crow, 2000: 44).

33 Cleft lip with or without cleft palate (NSCL/P) affects "1 in 700 - 1,000 newborns" annually in the U.S. and such a congenital craniofacial defect has become increasingly common in newborns (Beiraghi et al., 2007).

34 Gametogenesis is known as the process whereby cells experience meiosis to form gametes in the sexual reproduction to create a zygote (ThoughtCo., 2020). Every oocyte undergoes 23 chromosome replications in total (i.e., "22 germ-cell divisions and two meiotic divisions"), but there is no DNA replication in the last meiotic division (Ibid., 421).

35 On average, 840 spermatic chromosome replication events by the male's age of 50 (Conti and Eisenberg, 2016: 421; Vogel and Motulsky, 1997; Kong et al., 2012).

36 Deak et al., 2010.

37 The data available in the CDC Natality Registry are "derived from [live] birth certificates issued" from the 2016 to 2019 years (CDC, 2020).

38 The method of analysis is logistic regression using the Stata 17.0 computer program (StataCorp., 2021).

39 Independent Variable 1: (APA ≥ 35 years)

1. APA 1 Independent Variable 2: (AMA ≥ 35 years)
2. AMA Independent Variable 3: (APA ≥ 35 years * AMA ≥ 35 years)
3. Interaction Effect of APA 1 and AMA Independent Variable 4: (APA ≥ 50 years)
4. APA 2 Independent Variable 5: (APA ≥ 50 years * AMA ≥ 35 years)
5. Interaction Effect of APA 2 and AMA

40 To determine the link between advanced paternal ages and the three congenital anomalies, I restrict my observations to include only the known/reported ages of both parents found within the Natality

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Registry database (2020) to examine the reported congenital anomaly (i.e., Down syndrome, cleft lip, and/or spina bifida) of each live birth from 2016-2019.

41 Using the CDC Natality Registry (2020), I use observations that include disclosed age ranges of both partners (i.e., paternal age and maternal age) to include the father's age range. Paternal age ranges are distributed into eight groups that begin from 15 years of age (with five-year intervals): 15 – 19 years; 20 – 24 years; 25 – 29 years; 30 – 34 years; 35 – 39 years; 40 – 44 years; 45 – 49 years; 50 – 54 years; and 55 – 98 (CDC, 2020:15). In the APA ≥ 35 years variable, the father's age range grouped below 35 years [P < 35 years] is coded as "0", and the father's age range equal to or greater than 35 years [APA ≥ 35 years] is coded as "1". In the 50 years and above variable, the father's age range grouped below 50 years [P < 50 years] is coded as "0", and the father's age range equal to or greater than 50 years [APA ≥ 50 years] is coded as "1". The conceptualized advanced paternal ages (i.e., APA ≥ 35 years and APA ≥ 50 years) are both binary variables (0, 1).

42 Using the CDC Natality Registry (2020), I use observations that include disclosed age ranges of both partners (i.e., paternal age and maternal age) to include the mother's age range. Eight maternal age groups starting from 15 years of age (with five-year intervals) are identified: 15 – 19 years; 20 – 24 years; 25 – 29 years; 30 – 34 years; 35 – 39 years; 40 – 44 years; 45 – 49 years; and 50 – 54 years (CDC, 2020:13). Like the APA coding method, once the maternal age groups are identified, they are coded accordingly: if the mother's age range is less than 35 years [M < 35 years], then it is coded as "0"; and if the mother's age range is equal to or greater than 35 years [AMA ≥ 35 years], then it is coded as "1". The AMA is a binary variable (0, 1).

43 While the advanced paternal age begins at 35 years considering the 540 spermatic replications (Grewal et al., 2012), Vogal and Motulsky (1997) suggest that a male undergoes 840 spermatic replications by the age of 50 years—increasing the transcription errors throughout the replication process (Penrose, 1955). Thus, I include two more independent variables that include advanced paternal age of 50 years.

44 United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention" "(CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics, Natality public-use data 2016-2019, on CDC" WONDER Online Database, October 2020. Accessed at http://wonder.cdc.gov/natality-expanded-current.html on Jun 6, 2021, 1:24:47 PM."

45 United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention" "(CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics, Natality public-use data 2016-2019, on CDC" "WONDER Online Database, October 2020. Accessed at http://wonder.cdc.gov/natality-expanded-current.html on Jun 6, 2021, 1:29:36 PM."

46 United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention""(CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics, Natality public-use data 2016-2019, on CDC" "WONDER Online Database, October 2020. Accessed at http://wonder.cdc.gov/natality-expanded-current.html on Jun 6, 2021, 1:07:36

47 The frequency data that reflect statistical significance suggest a causal relationship between the respective dependent and independent variables.

48 Hassold et al, 1996; Thompson, 2019.

49 Predicted probabilities are the probability or likelihood of an event (i.e., Down syndrome, cleft lip with or without cleft palate, and spina bifida) that is calculated from the available data (StataCorp., 2021).