The Impact of Advanced Paternal Age on Autism, Schizophrenia, and other Neurological Disorders: A Literature Review

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Introduction

Autism Spectrum Disorder is a chronic disorder with onset by age three and is characterized by challenges with social skills, repetitive behaviors, speech, as well as with nonverbal communication (American Psychiatric Association, 2013). The rate of children being born with Autism Spectrum Disorder has significantly risen from 1 in 110 in 2006 to 1 in 54 in 2016 (Centers for Disease Control and Prevention [CDC], 2020) and in recent years, there has been much research dedicated to investigating the cause. Schizophrenia is another neurological disorder, typically diagnosed during one's mid-teens and mid-thirties that involves continuous patterns of delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior (American Psychiatric Association, 2013). Schizophrenia is one of the top 15 leading causes of disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators) and while the exact causes of both of these neurological disorders are unknown, most research agrees that there is a strong genetic component as well as an environmental influence. Nonetheless, there is always more research to be done regarding stronger or weaker causation factors in order to be able to provide clues to the biological pathways leading to these neurological disorders.

Simultaneously, the average paternal age in the United States has also increased in recent years. There was a study that analyzed data from more than 168 million U.S. births over a four-decade period and found that the average age rose from an average age of 27.4 in 1972 to 30.9 in 2015 (Khandwala, Zhang, Lu, & Eisenberg,2017). This study also found that

in 2015, men of Japanese and Chinese descent were, on average, 35 to 36 years old at the time of their child's birth while African-American and Hispanic fathers tended to be around 30 years old at the time of their child's birth. Furthermore, the average age of fathers with a college degree was 33 years old (Khandwala et al.,2017).

This is important because postponed parenthood may have a negative association with the cognitive ability of offspring. While previous research has mandated that older mothers are more likely to have children with chromosomal abnormalities, such as Down syndrome, there is room to delve further into potentially seeing if male fertility has played a significant role in this process as well. Furthermore, it is imperative to delve into the specific area of neurological disorders, such as autism and schizophrenia, and to research whether these disorders can be grouped together within this category.

An older pregnancy comes with a higher risk of mutation within the mother's egg. This is because a woman is born with her full supply of oocytes and meiosis is halted at metaphase II until fertilization. Therefore, the longer a woman waits to fertilize her eggs, the more her existent eggs naturally decrease in quality and in quantity, as she is exposed to radiation or harmful chemicals throughout her menstrual cycle. On the other hand, it has been said that men do not face this issue as men typically produce new sperm cells continuously throughout their lifetime. Yet, there remains a need to attend to male fertility and its impacts on their offspring since whereas eggs only divide when they mature in the ovaries (making their mutation rate more stagnant), sperm are continuously made throughout one’s lifetime and therefore generate new genetic material, some of which are subject to environmental hazards, radiation, and chemicals. Studies suggest that a father's age at the time of conception

might pose health risks for a baby since these mutations may be inherited by the offspring and may potentially have negative effects on their health. However, this field of research is still relatively small and results have been mixed. Therefore, further research is necessary.

The influence of maternal age on fertility, postnatal outcome of offspring, and the complications involved has also been thoroughly investigated, and these aspects have been clinically applied during fertility and pregestational counseling. On the other hand, the field of the reproductive outcome of male aging has gained relatively less traction. Therefore, this paper seeks to investigate and analyze the research on the impact the father's age can have on neurological disorders in offspring. The aim of this paper is to review the research into advanced paternal age at childbearing and the offspring's risk of the development of psychiatric disorders.

The Process of Sperm Formation (Spermatogenesis)

Human spermatogenesis, the process of sperm formation, is a complex, multifaceted biological process that is essential for a better understanding of this paper and to ultimately, advance research regarding male infertility. This six-step process of cellular events (Cheng, Wong,Yan, & Mruk, 2010) occurs in the seminiferous tubules of the testis and there are two main types of cells that are involved in spermatogenesis. The first type is the germ cell that eventually develops into sperm, and the second is the somatic cell called the Sertoli cell that nurtures the germ cells throughout the process of development.

Spermatogenesis begins with spermatogonial stem cells creating undifferentiated spermatogonia, which through mitosis, then gives rise to diploid spermatocytes. This occurs close to the basement membrane of the seminiferous tubules (de Kretser, Loveland,

Meinhardt, Simorangkir, & Wreford,1998). After this, there is a transformation and differentiation of spermatocytes that results in two types of cells. The first type serves to replenish the stem cells while the second type differentiates into primary spermatocytes that are diploid in nature. Then, these diploid primary spermatocytes undergo meiosis I and morph into two secondary spermatocytes, which then undergo meiosis II, producing haploid spermatids. Afterwards, spermatids undergo spermiogenesis at the border of the lumen to eventually form spermatozoa that are functional, commonly called sperm cells. The final process is spermiation during which the mature spermatozoa shed their residual cytoplasm and move, with the help of the Sertoli cells, towards the lumen of the seminiferous tubules in order to then mature further in the epididymis.

These resulting sperm cells are haploid, allowing for the haploid egg cell to contribute the other half of the genetic material in fertilization. In humans, the progression from spermatogonial stem cells to mature sperm takes 65 days (Dym 1994) (Figure 1). Additionally, the unique shape of spermatozoa includes a condensed nucleus protected by an acrosome and an attached flagellum to enable motility, all allowing for precise contact with the oocyte.

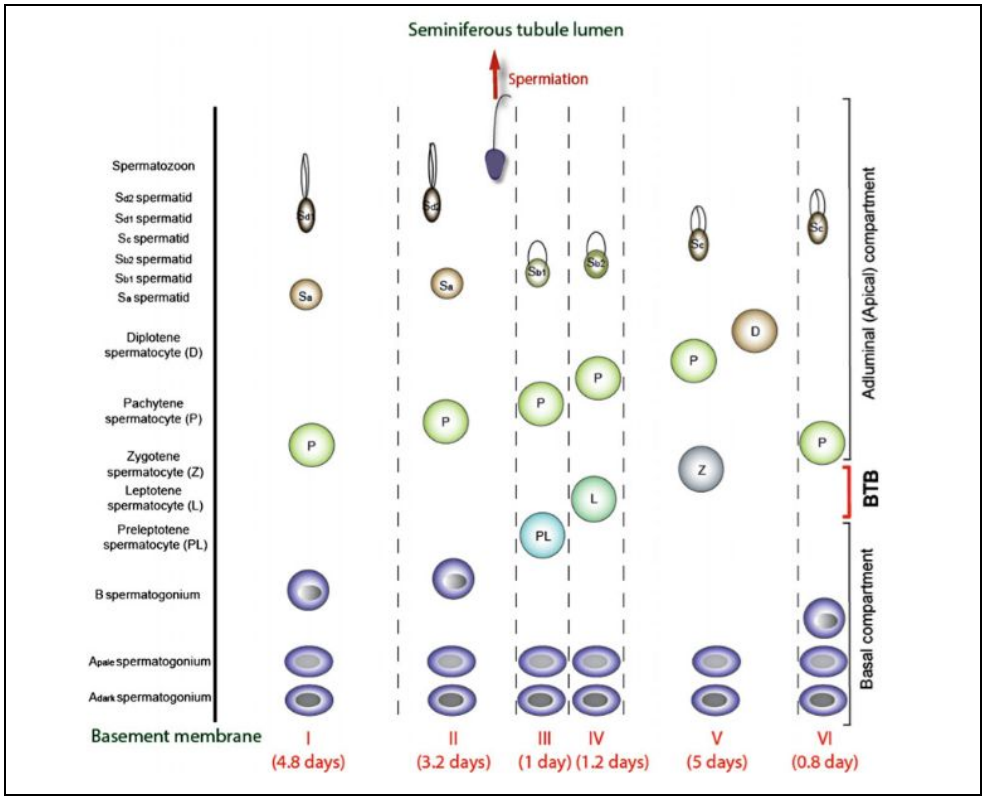

Figure 1 : The six stages of the seminiferous epithelial cycle (I-VI) in the human testis and the associated germ cell types in the seminiferous epithelium in each of these stages (Picture copied from Chen et al. 2017).

This process begins when a healthy male reaches the age of puberty, after which he produces about 200 million sperm daily. The initiation of spermatogenesis during puberty is typically thought to be regulated by the synthesis of BMP8B by the spermatogonia. This regulation is done through a positive feedback loop, meaning that once the amount of BMP8B produced reaches a critical concentration, the germ cells then begin to differentiate. The differentiation, in turn, produces high levels of BMP8B, and further stimulates the cell's differentiation (Gilbert, *Spermatogenesis* 2000). This was further proven through a study involving mice that demonstrated that mice lacking BMP8B do not initiate spermatogenesis at puberty (Zhao, Deng, Labosky, Liaw,& Hogan,1996).

Additionally, these processes are intricately controlled by regulatory hormonal and signaling systems, the most important of the regulatory pathways being the hypothalamic-pituitary–testicular axis (Chen, Mruk, Xiao,& Cheng, 2017). The pituitary cells regulate the production of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) which, in turn, regulate spermatogenesis since it is regulated through the control of FSH on Sertoli cells and LH on Leydig cells (Dalia,Ali,& Ghina,2019). This is a negative feedback system (Figure 2) because when levels of testosterone rise, the hypothalamus and anterior pituitary then inhibit the release of FSH and LH. The Sertoli cells also produce a hormone by the name of inhibin, which is released into the blood when the sperm count is too high. Inhibin also inhibits FSH release and causes spermatogenesis to slow down. Yet, this can be altered since if the sperm count ever reaches 20 million/ml, the Sertoli cells then stop releasing inhibin, and the sperm count increases (Avissar et al., *24.4. Hormonal Control of Human Reproduction* 2019).

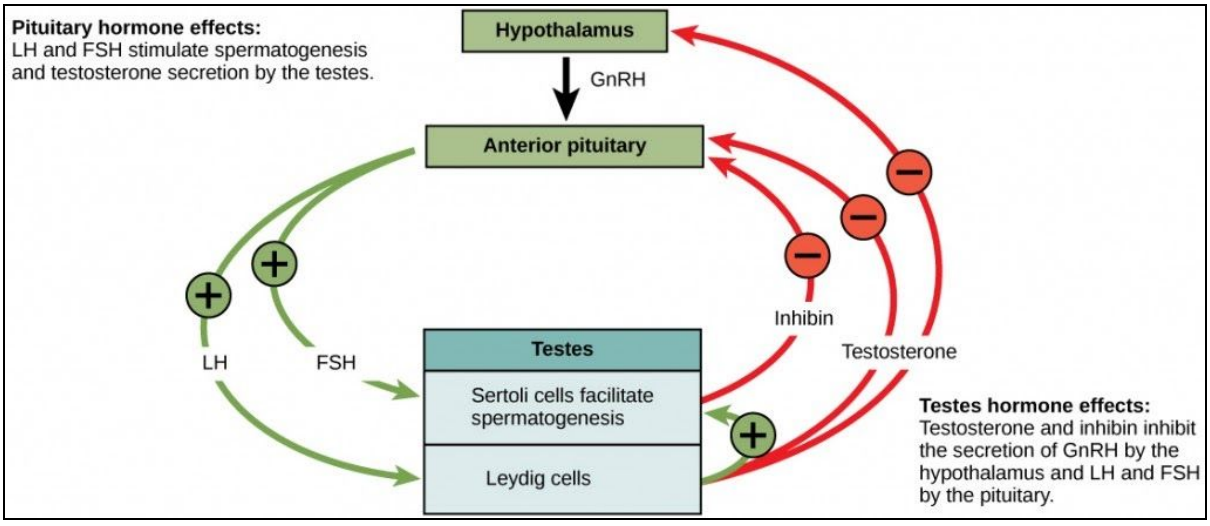

Figure 2. Hormones control sperm production in a negative feedback system (Picture copied from Avissar et al., *24.4. Hormonal Control of Human Reproduction* 2019)

Unlike female fertility, spermatogenesis and testosterone synthesis are lifelong processes that persist even into older age. Research has shown, however, that spermatogenic efficiency declines with age. This is measured by the spermatogenic index, meaning the number of spermatozoa produced per day per gram of testicular parenchyma. The reason that spermatogenic efficiency declines is because with age, there is an increase in the degeneration of germ cells throughout spermatogenesis (Weidner, Diemer & Bergmann, 2006). Additionally, it has also been proven that sperm motility, volume, and morphology are all known to decrease with aging (Hellstrom et al., 2006).

Other aspects of spermatogenesis that are impacted by age are DNA repeat extension mutations and that happens through mistakes in replication during proliferative stages of spermatogenesis (Pearson, Nichol Edamura, & Cleary, 2005). This is the result of spermatogenesis involving repeated rounds of DNA replication and cell division, generating a larger possibility for random mutational events to occur (Figure 3).

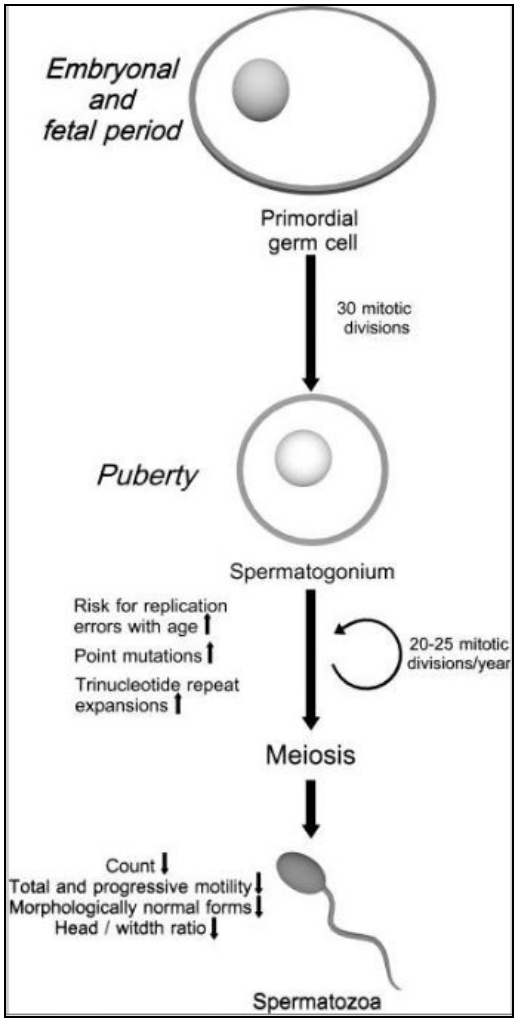

Figure 3. This figure depicts the cell divisions and possibilities for errors in spermatogenesis. As seen in the figure, during intrauterine development, primordial germ cells experience around 30 rounds of mitosis. Then, for each year after puberty, DNA replication continues and there are about 20–25 mitotic divisions. Furthermore, this figure shows how the primary source of point mutations in spermatozoa are errors during DNA replication. (Picture copied from Gunes, Hekim, Arslan, &Asci, 2016)

Paternal Age and its Impact on Offspring Morbidity

Many studies have delved into the topic of advanced paternal age on mutations in sperm and how this could negatively impact offspring, commonly called the paternal age effect. Early research found that paternal age can affect the number of mutations in an

offspring (Crow, 1997) and since then, research has only expanded and focused especially on de novo mutations. De novo mutations are changes in the DNA that arise spontaneously in egg or sperm cells around conception. Most people are born with many such mutations, and most of these changes are harmless though de novo mutations have been associated with autism (O'Roak et al., 2014).

The conversation about de novo mutations commonly focuses on the male as studies have demonstrated that de novo point mutations in offspring are mainly of paternal origin (Hehir-Kwa et al., 2011) and that the age-related increase in de novo mutations is over three times larger in males than in females (Goldmann et al., 2016).

Now, studies have shown that for every 16.5 years of paternal age, there was a doubling of the de novo mutation rate and that for each year increase in the father's age at conception, the number of mutations increased by about two (Kong et al.,2012). Moreover, this research demonstrated that older fathers are responsible for nearly all of a child's random genetic mutations. A father's age at conception may account for 97% of the de novo mutations found in his offspring (Kong et al.,2012), suggesting that the modern mutation rates may be primarily driven by the age at which fathers decide to have children. Indeed, in Iceland, the researchers hypothesized that those born in the year 2011 would have 17% more de novo mutations than those born in 1980 (70 mutations versus 60). Over that time period in that study, the average age of fathers rose from 28 to 33 (Kong et al., 2012).

A possible explanation for this is 'selfish spermatogonial selection', meaning that some pathogenic mutations result from a selfish mechanism that originates in aging testes. 'Selfish spermatogonial selection' refers to the system that favors the proliferation of germ

cells that carry pathogenic mutations. Therefore, this increasingly skews the mutational profile of sperm as men age and the result is an enrichment of de novo mutations in the offspring of older fathers (Goriely, McGrath, Hultman,Wilkie,& Malaspina, 2013).

This understanding, that older men harbor a greater number of mutations within their testes than younger men do, is in line with other detections of genetic decline. These measures range from clear signs of arrested germ cell divisions to complete involution of the seminiferous tubules (Paul & Robaire, 2013). Furthermore, research was able to trace back specific mutations that are linked to older age to individual germ cells within the seminiferous tubules (Maher et al., 2016).

So too, regarding neurological conditions, it was found that the disorders in the brain are likely to be most affected by de novo mutations (Gauthier & Rouleau, 2012) and that the paternal-age effect was specifically applicable to disorders that result from impaired brain function, such as autism, schizophrenia, and others (Saha et al.,2009). This is consistent with the fact that more genes are expressed in the brain than in any other organ, meaning that the fraction of new mutations that will affect its functions is the highest.

Another mechanism that may be behind the paternal age effect is the theory of epigenetic alterations, where impairments in epigenetic modifications result in altered chromatin structure and DNA-methylation patterns, which lead to altered gene expressions (Perrin, Brown, & Malaspina, 2007). A genome-wide DNA-methylation screen that compared sperm from young and old mice demonstrated a significant loss of methylation in the older mice in regions associated with transcriptional regulation. It also showed that there was a decrease in the DNA-methylation patterns of mice sperm throughout life and that this

decrease was reciprocal with brain gene expression alterations and behavioral problems (Milekic et al., 2015). Another similar longitudinal study in men 9–19 years apart strongly proposed that 139 genomic regions in the male human germline (cells that form the sperm) become increasingly hypo‐methylated with aging (Jenkins, Aston, Pflueger, Cairns,& Carrell, 2014). Therefore, these age‐related epigenetic processes in sperm could potentially also contribute to the paternal age effect.

Paternal Age and its Impact on Autism (and Schizophrenia)

Autism Spectrum Disorder and Schizophrenia are known to be caused by a combination of genetic and environmental factors and one genetic factor that has been of much study in recent years has been mutations within the father's sperm. For structural purposes, this section will mainly discuss autism while schizophrenia will be discussed more in depth later in the paper.

Research has investigated in depth the linkage between advanced paternal age and autism, generating many different nuances within the discussion. Some studies report a steady increase in risk with increase in age, and others depict a pronounced increase at a threshold of a certain age. There is research that simply indicates a link between older aged-fathers and neurological disorders such as autism spectrum disorders and schizophrenia (Mcgrath et al., 2014) while others found that older men are more likely than younger ones to have children with autism or schizophrenia since they pass on significantly more random genetic mutations to their offspring that increase the risk for these conditions (Kong et al., 2012). Another study found that 15% of autism cases in families with no other affected children were linked to de novo mutations in either the sperm or the egg that joined during

conception (Szalavitz, *Autism Studies Confirm Genetic Complexity and Risk for Older Fathers,* 2012). This overall confirmed prior research suggesting that older fathers' sperm is more likely to carry these mutations. In one study, researchers found that the mutations were four times more likely to occur in the fathers than in the mothers if the father was aged 55 or older (Hultman et al., 2011).

Additionally, this study proposed that men aged fifty or older were twice as likely to have children with autism than fathers under the age of thirty. It controlled for documented autism risk factors, including family psychiatric history, perinatal conditions, infant characteristics and demographic variables and through a 10-year birth cohort, autism risk was found to have increased monotonically with increasing paternal age. It also included a within-family analysis of discordant siblings that showed that affected siblings had older paternal age. This experiment also conducted a meta-analysis, demonstrating that there was an association between advancing paternal age and increased risk of autism across multiple studies. Biological mechanisms such as de novo aberrations and mutations or epigenetic alterations associated with aging were listed as possible roots of this association as discussed earlier (Hultman et al., 2011).

Another research studied people born in Israel over six consecutive years and found that there was a significant monotonic association between advancing paternal age and risk of autism spectrum disorder (Reichenberg et al., 2006). Offspring of men 40 years old or older were 5.75 times more likely to have autism spectrum disorder than children of men who were younger than 30 years old, and this remained true even after various factors were controlled for, such as year of birth, socioeconomic status, and maternal age. Additionally,

from the research, it seemed that the possible biological mechanisms behind the association were de novo mutations specifically associated with advancing age or alterations in genetic imprinting.

Some even propose that the risk seems to begin as early as at the age of 35 and that it continues to rise with parental age (Byars & Boomsma, 2016). This was found through probing health histories of more than 1.7 million people born between the years 1978 and 2009. Once the individuals with autism or schizophrenia were grouped by the age of their parents at time of their birth, the researchers measured how the numbers of autism and schizophrenia cases varied with the parents' ages. The results regarding schizophrenia will be discussed later in the thesis but the analysis revealed that children born to men aged 35 to 60 were up to 24 percent more likely to have autism than children with fathers aged 31 to 34. In line with this trend, this study also found that parents who were 15 to 30 years old were the least likely to have a child with autism; men in this age group had up to a 14 percent lower chance and women in this age group had a 17 percent lower chance than parents in their early 30s.

Other studies propose a later age of 45 and above (D'Onofrio et al., 2014). This was found through a population-based cohort study in Sweden, where researchers found (through comparing differentially exposed siblings, cousins, and first-born cousins among using other quasi-experimental designs) that advancing paternal age was associated with an increased risk for autism, along with other neurological disorders such as psychosis and bipolar disorder. Upon further analysis of the research, advancing paternal age was identified to even having had a dose-response relationship with every index of morbidity within sibling

comparisons, and the magnitude of the associations were larger than estimated (D'Onofrio et al., 2014). These results are consistent with the hypothesis that states that new genetic mutations occurring during spermatogenesis,that are much more frequent within men as they age, are causally related to offspring morbidity.

Along with the topic of mutations shared by advanced paternal age and the onset of autism, studies have also shown there to be a decreased variance in gene expression which has been one of the causal factors of paternal age-dependent autism. This is caused by mutations in transcription factors that serve to regulate gene expression and are associated with neurodevelopmental disorders in sporadic cases of autism spectrum disorder (Wiener-Megnazi, Auslender, & Dirnfeld, 2012). One study used micro-arrays to evaluate the expression levels of over 47,000 transcripts from children with and without autism. The study found that there is a decrease in the variance in the distribution of gene expression levels in lymphocytes in the children with autism and in increased paternal age. Gene expression pathways involved in transcriptional regulation were also found to be downregulated in the blood of children with autism and children of older fathers (Alter et al., 2011).

While it is possible to argue that this is not merely about older fathers but that the increased risk for autism and schizophrenia are present in younger mothers as well (Mcgrath et al., 2014), these increases stem from different roots. The risk related to younger mothers has been found to stem mainly from psychosocial, cultural or resource-mediated factors (Byars & Boomsma, 2016) while the risk related to older fathers stem mostly, if not solely, from biological factors and ultimately, has larger implications on the field of male fertility.

Other studies have expanded the conversation and incorporated the prospect of grandparental age factoring into the equation. Through a population-based, multigenerational, case-control study in Sweden, advanced grandparental age was found to be related to an increase in risk of autism spectrum disorder in offspring, suggesting that the risk of autism spectrum disorder could develop over a span of multiple generations. These results are also consistent with the notion that mutations and/or epigenetic alterations are associated with advancing paternal age (Frans et al., 2013). Furthermore, as expressed by other research studies, this is in line as well with information laid out within the topic of Mendelian inheritance since the mutagenic load in paternal spermatogonia would progressively accumulate in the following generations, thereby increasing the risk of autism and schizophrenia in both children and grandchildren of men who were old at conception (Janecka et al., 2017).

On the other hand, within the research, one study felt that there was more of a maternal link (Idring et al., 2014). Though advancing parental age was found to increase the risk of autism spectrum disorder in children as was found in much of the other literature, the risk of autism was greater for older mothers as compared with older fathers. Upon its analysis, the increased risk due to advancing paternal age was more dependent on the mother's age at the time than the increased risk due to advancing maternal age was contingent on the father's. The maternal age effects, however, were non-linear, while the paternal age effects displayed linearity and ultimately showed that there was more of a direct relationship between paternal age and increased risk as opposed to insignificance in statistics and random results. This study added another nuance to the discussion on this topic, namely

that advancing parental age was more strongly associated with autism spectrum disorder when it included intellectual disabilities than autism spectrum disorder without the intellectual disabilities.

Schizophrenia

Advanced paternal age can have different impacts on different types of neurological disorders and therefore, it is important to discuss if the pattern that is seen in autism spectrum disorder could be applicable to schizophrenia as well.

It is first necessary though to compare these disorders themselves and since there is, in fact, phenotypic and genetic overlap between autism spectrum disorder and schizophrenia, there may then be more to discuss regarding the associations between them and advanced paternal age. Both autism and schizophrenia are characterized as neurodevelopmental disorders and include social impairment (Lugnegård, Hallerbäck, Hjärthag, & Gillberg, 2013) and behavioral rigidity (Hommer & Swedo, 2015). There are also some similarities in brain activity. For example, in both schizophrenia and autism spectrum disorders, there is reduced frontolimbic and superior temporal sulcus engagement which contributes to social cognition deficits (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). This similarity is present as well in terms of brain volumetrics, potentially reflecting shared etiological mechanisms (Cheung et al., 2010). The relevance of these similarities were brought to light through various studies that demonstrated that a family history of both schizophrenia and of bipolar disorder was a risk factor for autism (Sullivan et al., 2012) and that an early diagnosis of autism was actually likely to increase the chance of developing schizophrenia at a later age (Selten,Lundberg,Rai,& Magnusson, 2015). Ultimately, a more direct genetic correlation

between these disorders exists and has been confirmed by research (Lee et al., 2013). Yet, throughout the literature, there is slightly more of an ambiguous relationship between advanced paternal age and schizophrenia.

On a whole, most of the research has indicated a relationship between advanced paternal age and schizophrenia but has rejected the de novo hypothesis regarding schizophrenia, distinguishing it from the correlation between advanced paternal age and autism.

Firstly, schizophrenia was found to have significant associations for fathers above the age of 35 years old (Buizer-Voskamp et al., 2011) . It was also suggested that the higher the paternal age at his first child's birth, the higher the incidence rate ratio of schizophrenia, especially if the age is over 50 years old (Pederson, Mcgrath, Mortensen, & Peterson, 2014). This means that the results were less significant when discussing paternal age at the birth of the subject under study and also indicated that there could be more than just de novo mutations involved in the correlation. Another study as well rejected the idea that de novo mutations play a large role in the link between advanced paternal age and schizophrenia (Peterson, Mortensen, & Pederson, 2011). This study argued that if the risk of schizophrenia was primarily driven by paternal age-related de novo mutations, then this process would be found across the reproductive lifespan of the father, regardless of the age of the father when he had his first child, but the findings have suggested that this was not the case (Peterson et al., 2011).

An interesting aspect of the research regarding advanced paternal age's impact on schizophrenia is that, similarly to autism, it can be passed through generations and that

grandparental age can be a factor as well (Frans et al., 2011). This study also found that the age of the maternal grandfather was associated with offspring schizophrenia but that the age of the paternal grandfather was not.

Another interesting facet is that while many have rejected the de novo hypothesis, there have not been many other potential causational factors put forth as seen by a study run on 463 families with an affected offspring and multiple biological siblings (Jaffe, Eaton, Straub,Marenco,& Weinberger,2014). Furthermore, one meta-analysis study researched six cohort studies and six case-control studies and found that there was a significant increase in risk of schizophrenia in the offspring of older fathers, above the age of 30 and especially above the age of 50, as compared to a reference paternal age of 25-29 (Miller et al.,2011) but that the mechanism of these associations is not known. It also added that this risk factor only increases the risk of schizophrenia as much as any single candidate gene of risk and that it is not a definite causation. This link between advanced paternal age and schizophrenia was strong across different ethnicities (Naserbakht,Ahmadkhaniha,Mokri,& Smith,2011)(Lampi et al., 2013) and remained significant even after possible confounds were controlled for , such as socio-economic status, age of the mother, and paternal psychiatric morbidity.

On the other hand, there have been some research studies that have not found a link between advanced paternal age and schizophrenia. One study found that for schizophrenia, the increased risk was limited to those born to mothers in their teens or early twenties but that researchers did not find a link between the father's age and the risk of schizophrenia (Byars & Boomsma, 2016).

Overall, more research must be done regarding this relationship between advanced paternal age and schizophrenia to establish if there is even a link and if so, what the mechanism of association is.

Other Neurological Disorders

Though not as intensely studied, it is important to briefly discuss the potential impact of advancing paternal age on a few other neurological disorders as well.

The research on bipolar disorder, for instance, has been relatively balanced in its findings. On the one hand, children of men aged 55 years and older were found to be 1.37 times more likely to be diagnosed as having bipolar disorder than the offspring of men aged 20–24 years (Frans et al., 2008). Another study confirmed this as well, with the nuance of it being bipolar disorder with psychotic symptoms (Lehrer et al., 2016). In contrast, other research did not find any association between paternal age and bipolar disorder (Buizer-Voskamp et al., 2011) and this finding was present in another study as well (Mcgrath et al., 2014).

Additionally, there was one study that found that advanced paternal age increased the risk for obsessive-compulsive disorder (Wu et al., 2012) but more research is needed to corroborate this data.

Regarding attention deficit hyperactivity disorder (ADHD), while there has been little evidence, some studies have shown there to be an association between ADHD and advancing paternal age (D'Onofrio et al., 2014). Mcgrath et al., (2014) indicated as well that overall, paternal age was associated with an offspring's risk of having ADHD but that the results

suggested that both younger and older fathers had an increased risk of having a child with ADHD and that the increased risk was greater in younger fathers.

Future research in these areas can expand the conversation significantly and can potentially further highlight the risks associated with advanced paternal age.

Limitations

Until this point in the thesis, the research has overwhelmingly been one sided. Meanwhile, there has been research, in fact, that does not support the correlation between advanced paternal age and autism or other neurological disorders. One major study performed in 2016 found that the mutations that men accumulate in their sperm as they age do not account for most of their increased risk of having a child with autism. Instead, men who carry risk factors for having a child with autism simply tend to have children later in life (Gratten et al., 2016). The researchers findings suggest that de novo mutations in sperm account for, at most, 20 percent of the increased risk for autism and schizophrenia associated with the father's advanced age, which cannot really explain the increase in risk that has been said to be present. Through utilizing mathematical methods, the study was able to determine that a father's age-related mutations accounted for only about 10 percent of the increase in autism risk due to paternal age.

A Swedish study came to a similar conclusion through researching the association between parental age and intelligence quotient in over 500,000 Swedish men and indicated that advanced paternal age showed no association with offspring IQ (Myrskylä, Silventoinen, Tynelius, & Rasmussen, 2013).

Sociological component

Thus far, this paper has focused on the impact of fathers being older on their offspring. Yet, how did society get to this point? Why are men having children later and what are the sociological underpinnings of these reasons?

Studies have shown that perhaps some of the factors leading to a rising trend of having children later are factors such as the increased availability of contraception, as well as the increased entry of women into the workforce (Khandwala et al.,2017). Additionally, assisted reproductive technologies have become more accessible to the general population, enabling older couples to hope that they can fulfill their aspirations for healthy offspring later in life (Wiener-Megnazi et al., 2012).

Another sociological tendency that advanced this trend as well was the value shift within Western society. Parenthood has increasingly become an issue of personal preference, and many have chosen to be voluntary childless or at least postpone parenthood until a period in life when raising children is more consistent with one's chosen career path or other life goals (Mills,Rindfuss,McDonald,& Te Velde, 2011). More unstable relationship patterns and precarious work situations have also contributed to this (Mills et al., 2011). Furthermore, due to increased individualization, people rely more on outside institutions than the family to provide security (Little, *Chapter 14. Marriage and Family* 2016). Yet, there are possible social disadvantages of increased paternal age that should also be considered, such as less energetic parents and decreased likelihood of the child benefiting from long term relationships with grandparents (Bray, Gunnell, & Smith,2006).

Discussion

The simultaneously rising rates of autism and other neurological disorders and the average paternal age have caused reason to investigate further into whether there is an association between the two. Another motivation for exploring this topic is that typically, the mother is labelled as the primary contributor to disorders in offspring and that only her age matters regarding rates of passing on mutations. Yet, if a link would be found between advanced paternal age and the prevalence of neurological disorders, this could expand that conversation to include the father as well and shift the discussion of fertility to being a shared responsibility on both parents.

Through the research, it was shown, in fact, that specifically the age of the father, as opposed to the mother, impacted the number of mutations in offspring and particularly increased the amount of de novo mutations (Hehir-Kwa et al., 2011) as well as strengthened the rate of epigenetic alterations (Jenkins et al., 2014). This paper focused solely on neurological disorders as genes are expressed most in the brain so the fraction of new de novo mutations affect its functioning most (Gauthier & Rouleau, 2012).

The risk of a child having autism spectrum disorder was overwhelmingly found to be enhanced by having an older father. The age that classified an ‘older father’ was disputed in the literature and spanned anywhere from 35 (Byars & Boomsma, 2016) to 55 (Hultman et al., 2011) and even spanned multiple generations (Frans et al., 2013).

The conversation around schizophrenia followed in a similar direction and shared the same age of 35 at which the child becomes at risk (Buizer-Voskamp et al., 2011). Some even ventured to propose that the risk starts at 30 and significantly increases after the age of 50

(Miller et al.,2011) . Yet, there was more ambiguity regarding the association of an advanced paternal age and schizophrenia and while some said that de novo mutations do not contribute to this association (Peterson et al., 2011), others claimed that the mechanism is unknown altogether (Jaffe et al., 2014). Similar to the research regarding autism, grandparental age can play a role as well in offspring's risk for schizophrenia (Frans et al., 2011).

There was not much unified research regarding other neurological disorders but research speculated there to be a link between an advanced paternal age and other neurological disorders, such as bipolar disorder (Frans et al., 2008), obsessive-compulsive disorder (Wu et al., 2012), and attention deficit hyperactivity disorder (D'Onofrio et al., 2014).

Two research studies challenged these understandings and instead proposed that instead of the sperm of an older man being the root cause of autism or other neurological disorders in offspring, men who carry risk factors simply tended to have children later in life for other reasons (Gratten et al., 2016) or that simply there was no association between advanced paternal age and the IQ of offspring (Myrskylä, et al., 2013).

The paper then transitioned to discussing the sociological motivations behind the increase in paternal age. These included the availability of contraception, entry of women into the workforce, the advancement of reproductive technology, a general value shift within society, and others.

This topic has many important ramifications on the perspectives of fatherhood and on the flexibility of beginning that new stage of life. Until this point, men have had the choice to delay having children for any reason they find convincing. The general notion within society

has always been, as quoted in the New York Times, “Whereas a woman’s clock typically slows in her 30s and runs down by age 50 or so, it can go on ticking almost indefinitely for a man. Witness these celebrities — George Clooney, Hugh Grant, Steve Martin, David Letterman and John Stamos — who became first-time dads in their 50s or beyond” (Brody, *The Risks to Babies of Older Fathers* 2019). That view was generally unchallenged until now. This data strongly suggests that paternal age matters as well and though advanced paternal age does not have identical effects as advanced maternal age, it still significantly contributes to the health of the baby. In fact, one study even concluded that over 12 percent of adverse outcomes in births to fathers aged 45 years or older could have been prevented if the fathers were younger (Khandwala et al., 2018).

These findings challenge traditional views on male fertility and reproduction and question the notion that women are the only ones with a so-called “biological time clock”. Additionally, by proving that it is not solely the mother's age and health that impacts the potential fetus, there will be a shift in the dynamic surrounding discussions of fertility.

Recommendations for future research would include corroborating previous data and investigating the mechanisms behind the associations in order to truly detect if paternal age impacts the psychiatric morbidity of offspring. One way this could be done is by performing polygenetic risk score profiling through genetic data. Then, these polygenetic risk scores can be employed to investigate if men with higher polygenetic risk have children at later ages, meaning that men who are more likely to have children with any of these disorders simply had children at later ages anyway or if there is an inherent link between age and the discussed risk. This method of testing has already provided evidence for a relationship between genetic

factors associated with risks of schizophrenia and with the age of first maternity (Mehta et al., 2016).

If, however, based on the presented research and future research, it is confirmed that the paternal-age effect on the rate of de novo mutations does, in fact, lead to substantially higher chances of neurological disorders in children of older fathers, another possible recommendation could include collecting the sperm of young adult men and cold-storing it for later use (Kondrashov, 2012).

Another recommendation, based on the findings and implications of this paper, was made by Dr. Hilary K. Brown in 2018 who suggested that doctors begin to stress to everyone of reproductive age just how important it is to adopt a healthy lifestyle, and not just discuss it with women. In turn, this will increase the general awareness of the man's responsibility to reproductive health (Brody, *The Risks to Babies of Older Fathers* 2019)(Brown, 2018).

Everyone who desires to be a parent imagines what parenthood will look like and what type of life they would like for their future child. Given the plethora of research supporting an association between older fathers and autism, schizophrenia, and other neurological disorders, it would be advisable for men to begin having the conversation of family planning at a younger age and to keep this research in mind in order to try and ensure to the best of their ability, that their dreams can become a reality.

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