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REVIEW ARTICLE

A multifactorial model for the etiology of neuropsychiatric disorders: the role of advanced paternal age

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Mental or neuropsychiatric disorders are widespread within our societies affecting one in every four people in the world. Very often the onset of a mental disorder (MD) occurs in early childhood and substantially reduces the quality of later life. Although the global burden of MDs is rising, mental health care is still suboptimal, partly due to insufficient understanding of the processes of disease development. New insights are needed to respond to this worldwide health problem. Next to the growing burden of MDs, there is a tendency to postpone pregnancy for various economic and practical reasons. In this review, we describe the current knowledge on the potential effect from advanced paternal age (APA) on development of autism spectrum disorder, schizophrenia, attention-deficit/hyperactivity disorder, bipolar disorder, obsessive-compulsive disorder, and Tourette syndrome. Although literature did not clearly define an age cut-off for APA, we here present a comprehensive multifactorial model for the development of MDs, including the role of aging, de novo mutations, epigenetic mechanisms, psychosocial environment, and selection into late fatherhood. Our model is part of the Paternal Origins of Health and Disease paradigm and may serve as a foundation for future epidemiological research designs. This blueprint will increase the understanding of the etiology of MDs and can be used as a practical guide for clinicians favoring early detection and developing a tailored treatment plan. Ultimately, this will help health policy practitioners to prevent the development of MDs and to inform health-care workers and the community about disease determinants. Better knowledge of the proportion of all risk factors, their interactions, and their role in the development of MDs will lead to an optimization of mental health care and management.

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IMPACT:

- We design a model of causation for MDs, integrating male aging, (epi)genetics, and environmental influences.
- It adds new insights into the current knowledge about associations between APA and MDs.
- In clinical practice, this comprehensive model may be helpful in early diagnosis and in treatment adopting a personal approach. It may help in identifying the proximate cause on an individual level or in a specific subpopulation. Besides the opportunity to measure the attributed proportions of risk factors, this model may be used as a blueprint to design prevention strategies for public health purposes.

INTRODUCTION

According to the World Health Organization (WHO), one in four people in the world will be diagnosed with a neurological or mental disorder (MD) at some point in their lives.[1] In 2017, worldwide 970 million people experienced a MD, including depression (264 million people), anxiety (284 million people), attention-deficit and hyperactivity disorder (ADHD) (73 million people), autism spectrum disorder (ASD) (31 million people), and schizophrenia (SCZ) (20 million people).[2] Other diagnoses included eating disorders, substance use disorders, and idiopathic intellectual disabilities. These rising numbers are particularly problematic. Not only because health-care systems are facing unprecedented challenges but also because many MDs arise in childhood or adolescence and need better attention.[2]

First, in a large part of the world, adequate diagnosis and treatment for MDs (at any age) is not considered a main priority in health care. For example, the Regional Office for Africa of the WHO collects data on communicable diseases such as HIV and tuberculosis, and data of noncommunicable diseases such as cancer and diabetes mellitus, but there are no data of incidences or mortality rates of MDs.[3] Moreover, mental health research is mostly performed in high-income countries, and results or approaches to therapy cannot simply be extrapolated to low- and middle-income countries.[4] Second, in most countries, including the Western World, health care is not yet adequately organized to guide and care for children who develop a MD.[5] Service barriers and long waiting lists testify to the flaws in current health-care systems.[6,7] Third, children with a MD often receive a co-occurring diagnosis of another MD.[8] In spite of attempts to reach a consensus on treatment, lack of knowledge about the complexity of this group of disorders largely contributes to the fact that early signs are often missed and current treatment strategies fall short of guidelines.[9,10] Furthermore, current theories

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of disease etiology conceal risk factors and/or mechanisms of interactions that have not yet been explored.

Because the onset of mental illness generally occurs in childhood, research on potential risk factors has mainly focused on a number of childhood-related exposures, such as socio-economic setting, education, psychosocial environment, and even environmental exposures such as artificial food coloring.[11,12] Along with numerous environmental risk factors, genetic predisposition is also known to contribute to the development of MDs, such as ADHD.[13] Furthermore, the interaction of the environment (before and after birth) with the individual's genome is a new path to better understand the origin of these neurological disorders.[14] Timing of the exposure may determine if a (genetically predisposed) person will or will not develop a disorder.[15] For instance, Goyal and Miyan[16] suggest that one or more environmental insults are needed during the development of the neurological, immunological, and/or autonomic system to develop ASD. They propose a "variable insult model" where the sequence of the environmental insults determines which subtype of ASD a child may develop. Another new concept that generated considerable interest in literature is the influence of advanced parental age (APA). In recent years, there is a significant increase in life expectancy, marriage age, and the quest for economic stability that has led couples to postpone their pregnancy. In a Nature Medicine paper of 2008, Schubert[17] raised the problem of the biological clock of the male germline in aging men and the related effects on the increasing numbers of children with MDs. Although the author discussed studies where a cut-off age of 40 years was used, the risk for de novo mutations in the male germline increases every year of a man's life. Because advanced parental age at first childbirth is becoming increasingly prevalent in many nations, along with the rise of MDs in children, this new trend in our societies may have an important influence on public health in the future[18,19]

While most studies explore just one risk factor, and few examine the number of potential risk factors, to our knowledge, the literature fails to elaborate a comprehensive multifactorial model that is useful in research and clinic. In the current review, we address this shortcoming. Starting from the perspective that APA plays a role in the development of MDs, we design an integrative model of causation including current knowledge on genetics, epigenetics, and social or other parental or childhood environmental exposures (Fig. 1). This model may be helpful as a guideline for future epidemiologic research studies, health policy, and management. In the clinic, it may be valuable to identify the potential causes of the disease or to develop a tailored treatment plan for children with related phenotypes or diagnosis of a specific MD.

EPIDEMIOLOGIC RESEARCH CONCERNING APA-RELATED MDS

Although associations between APA and offspring health, including MDs, are widely established, the exact causative mechanisms are still unclear. Below we discuss several MDs using the Diagnostic and Statistical Manual of Mental Disorders (DSM) latest edition[20] that have been related to paternal age. Tables 1–6 present an overview of the literature discussed below by MD.

ASD refers to a range of neurodevelopmental conditions characterized by social skills impairment, delayed language development, and repetitive stereotyped patterns of interests and behavior.[21] Literature demonstrates a significantly higher risk for ASD in offspring of older fathers.[22,23] A 2017 meta-analysis shows that this risk begins to rise already from a paternal age of 35 years (odds ratio (OR) = 1.32; 95% confidence interval (CI): 1.20–1.45).[23] In the same year, a meta-analysis summarizing six cohort studies and 21 case–control studies show that each additional 10 years of paternal age is related to a 21% increase in risk for the offspring to develop ASD; pooled OR was 1.21 (95% CI: 1.18–1.24).[22] Most recently, Oldereid et al.[24] confirmed this positive association between APA and ASD. After analyzing eight case–control and eight cohort studies, they measured a pooled OR of 1.25 (95% CI: 1.20–1.30). Other recent cohorts and case–control studies, not included in the above-mentioned meta-analyses, provide additional evidence for an association between APA and offspring's ASD risk, as presented in Table 1.[25–29]

While most studies focus on APA effects on the first generation, few also explore transgenerational effects. Two large multigenerational studies, a Swedish case–control study (including 5936 cases and 30,923 controls) and a Danish cohort study (n = 820,672), showed partly conflicting results.[25,30] In the Swedish study of Frans and Sandin,[30] a monotonic association was found between ASD risk in grandchildren and age of the maternal and paternal grandfathers at the birth of the parent. The Danish study by Gao et al.[25] showed a significant but yet unexplained U-shaped relation. If the paternal grandmother was >40 years at conception, grandchildren were at risk to develop ASD; OR = 1.40 (95% CI: 1.03–1.90). A similar effect was seen in grandchildren from young paternal grandmothers; OR = 1.18 (95% CI: 1.04–1.34). If maternal grandfathers or grandmothers were younger than 19 years old at conception, an increased risk for ASD was also measured; ORs were 1.50 (95% CI: 1.26–1.78) and 1.68 (95% CI: 1.52–1.85), respectively.

SCZ is a severe MD, characterized by disruptions in thinking and language, perception, and the sense of self, including psychotic experiences and functional impairment (WHO, 2014).[31] In the above-mentioned extensive meta-analysis by Oldereid et al.,[24] a clear positive association was described between APA and SCZ (pooled OR = 1.31; 95% CI: 1.23–1.38). However, they criticized the low to medium quality of the studies included in their meta-analysis, due to possible confounding, differences in reference age categories, and poorly defined diagnosis. Similar results have been shown in a most recent and large population-based cohort study on 916,439 Israeli, confirming the link between APA and SCZ[32] (Table 2). A meta-analysis by Wohl and Gorwood of 2007 demonstrated an increased SCZ risk in offspring of both younger and older parents. In the latter age group, they found that regardless of the reference age used, the risk to father a child with SCZ was always significantly higher above the age of 35 years.[33] A significant positive association was also shown in another meta-analysis by Miller et al.,[34] showing an OR of 1.06 if fathers were young (<25 years old) or slightly older (>30 years old), versus a reference group of fathers between 25 and 29 years old. However, this effect increased with age; OR was 1.66 (95% CI: 1.46–1.89) if fathers were ≥50 years old (Table 2). When considering offspring sex, an effect of young paternal age (<25 years old) on the development of SCZ was only seen in sons (but not in daughters), while no such differential effect was observed in older fathers.[34] Two recent case–control studies also report that SCZ risk in offspring is increased in younger fathers[35] and in older fathers,[36] but no differences were found between male and female offspring.[32,34,36–38]

According to the current knowledge, it is still unclear if the relationship between paternal age and risk for SCZ is U-shaped or linear, and if the effects are sex-specific. This knowledge gap was also mentioned earlier by de Kluiver et al. in 2017, who stressed the need to further examine this issue concerning its importance in counseling future parents and public health.[39]

Transgenerational effects have been observed in one multigenerational case–control study (including 2511 cases and 15,619 controls), with a higher SCZ risk in grandchildren of maternal grandfathers aged ≥55 years at the birth of the parent. An OR of 2.79 (95% CI: 1.71–4.56) was measured, when compared to a reference group of grandparents aged 20–24 years at the birth of the parent. No sex-related effects were measured in this large study.[40]

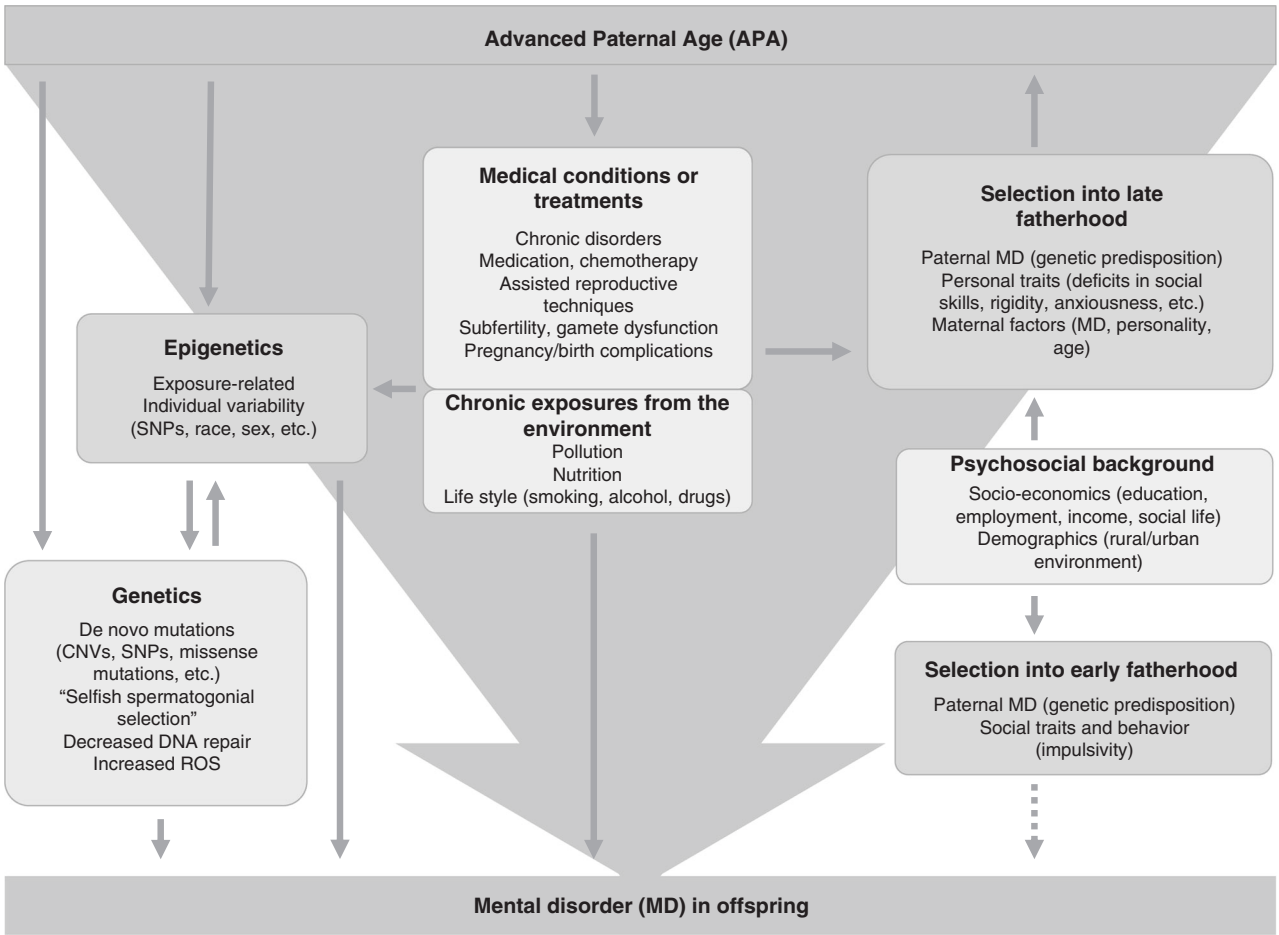

Fig. 1 Conceptual framework representing a hypothetical causal model for the development of mental disorders in children of advanced age fathers. Based on our interpretation of reports discussed in this review, we here show a comprehensive multifactorial model that includes the following components related to paternal age. (i) Genetic changes (orange frame): with advancing paternal age the risk for de novo mutations increases, DNA repair decreases, and/or regulation of antioxidant mechanisms fails (or ROS increases), leading to an increased genetic risk for MDs. (ii) Epigenetics (pink frame): with advancing paternal age, methylation status alters and epigenetic regulation and imprinting can derail in sperm cells; if inherited, this could lead to altered gene expression, influencing behavior in offspring. In addition, multiple exposures during life can alter the epigenome, further influencing offspring's disorder risk. Epigenetic aberrancies in the male germline could also increase mutability or trigger DNA damage, or alternatively, a de novo mutation may occur at a regulatory site, resulting in a "gene–epigene" interaction. Furthermore, susceptibility to epigenetic alterations can be influenced by genetic polymorphisms (arrow back from genetics to epigenetics).[14] (iii) Selection into late/early fatherhood (blue frames): due to genetic predisposition for MDs, certain personality or behavioral traits or a (sub)clinical psychiatric phenotype in men, can lead to delayed (or earlier) fatherhood as well as the same genetic predisposition in offspring. Note that in the case of early fatherhood (not the focus of this paper), there is obviously no link with APA (a dashed arrow shows an independent effect of young fatherhood on MD in offspring); "selection into late fatherhood" is a third variable (a confounder or an effect modifier). (iv) Environmental resources, including psychosocial environment, medical conditions, and other environmental exposures (green frames): on the one hand, APA is related to parenting skills and a stable financial or home situation, and on the other hand, APA can be related to social isolation and decreased communication skills. Therefore, it can be protective as well as risk enhancing for MD development in offspring. The association between APA and MDs in offspring can be confounded by multiple factors, including medical conditions or treatments, maternal age, race, paternal employment, pregnancy complications (fetal/placental growth retardation or gestation time), and other unknown or unmeasured factors. Note, not all possible arrows have been drawn given our focus was to better understand the role of APA in MDs. APA advanced paternal age, MD mental disorder, CNVs copy number variations, ROS reactive oxygen species, SNPs single-nucleotide polymorphisms.

ADHD is a neurodevelopmental disorder characterized by a pattern of inattention and/or hyperactivity and impulsivity. Generally, ADHD is known to affect mainly the offspring of young parents. A well-accepted reason for this has been described by Hvolgaard Mikkelsen et al.,[41] suggesting that the disorder in itself may increase social interactions (due to impulsive behavior), resulting in the early debut of sexual relationships. Hence, men with ADHD are more likely to have children at a younger age, compared to men without ADHD. Consequently, if genetically inheritable, early parenthood and ADHD in offspring may be associated when studying a potential link, but the actual cause for this correlation will not be age but a genetic factor together with an impulsive or social behavioral factor of the father. As age itself is not the causal factor, this relationship is represented in the form of a dashed arrow in Fig. 1. As shown in Table 3, study results with regard to the effect of paternal aging on the development of ADHD in offspring are inconsistent, with some findings suggesting a protective effect[26,41] and others suggesting a risk-enhancing[42–45] or an insignificant (or no) effect of APA.[46–48] This inconsistency in results could be due to limited sample size, demographic differences, and confounding factors. None of the discussed articles made a separate analysis on children with a genetic predisposition to develop an MD (inherited from the parents) versus children with no clear predisposition to develop

Table 1. Association between paternal age and autism spectrum disorder in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Oldereid et al., 2018	Meta-analysis	Not mentioned (16 studies)	≤35 35–40 40–45 >45	1.07 1.14[a] 1.37[a] 1.43[a]	1.02–1.12 1.08–1.21 1.23–1.53 1.33–1.53	Maternal age
Wu et al., 2017	Meta-analysis	17,658,960	Lowest paternal age group Reference point Highest paternal age group	0.81[a] 1.00 1.55[a]	0.73–0.89 Reference 1.39–1.73	Individual studies corrected for either of the following factors: parental age difference, maternal weight, maternal diabetes, year of birth, birth order, educational level
Wang et al., 2017	Meta-analysis	12,119,050	≥ 35	1.32[a]	1.20–1.45	None
Gao et al., 2020	Cohort	1,476,783	<20 20–24 25–29 30–34 35–39 40–45 45–49 ≥50	1.00 1.01 1.00 1.02 1.11[a] 1.27[a] 1.35[a] 1.44[a]	0.81–1.20 0.95–1.07 Reference 0.98–1.05 1.07–1.16 1.20–1.34 1.24–1.47 1.27–1.64	Year of birth, parity, maternal country of origin, maternal education, maternal age
Janecka et al., 2019	Cohort	1,490,745	<27.5 27.5–32.5 32.5–37.5 >37.5	1.03 1.00 1.03 1.26[a]	0.99–1.08 Reference 0.99–1.07 1.20–1.32	Parity, sex, parental psychiatric history, maternal smoking during pregnancy, gestational age, parental immigration, maternal age
Merikangas et al., 2017	Cohort	8725	25–29 ≥30	1.00 1.028[a]	Reference 1.005–1.051	Sociodemographic factors, comorbid disorders, maternal age
Geetha et al., 2019	Case control	55 cases, 55 controls	<35 >35	1.00 2.703[a]	Reference Not mentioned ($p = 0.001$)	Environmental toxic exposure/air pollution during pregnancy, family history of ASD, epilepsy/seizures, consanguinity, stress during pregnancy, nutrition during pregnancy, labor mode, fetal hypoxia, NICU admission, history of breast feeding, maternal age
Khaiman et al., 2015	Case control	235 cases, 235 controls	<35 >35	1.00 3.55[a]	Reference 2.07–6.09	Low/unemployed maternal occupation, maternal history of autoimmune diseases, family history of neuropsychiatric disorders, maternal age

[a]Significant at $p < 0.05$.

an MD. This may be due to the fact that most observational studies are based on data drawn from national or medical registers (generally not designed to study the etiology of diseases).

Although the effect of paternal age is unclear, the above-listed literature concerning younger paternal age agrees in a positive association with ADHD, most likely because of social traits and inheritance of the disorder. This has been presented in Table 3.[26,41,42,44,49]

Bipolar disorder (BPD) is a chronic mood disorder consisting of both manic and depressive episodes, separated by periods of normal mood. To our knowledge, no meta-analyses have been performed to better understand a potential link between APA and BPD. However, one can cautiously detect a positive association with variable effect sizes from a few individual studies (Table 4). A 2008 case–control study by Frans et al.[50] showed a steady significant result for fathers aged 30 years or older with an OR ranging from 1.09 to 1.37. This has been partly confirmed by a cohort study of Weiser et al. in 2020, who found a significant increase in risk for BPD with advancing paternal age; but, after adjusting for paternal age at birth of the first child, this effect disappeared.[32] Similarly, Byars and Boomsma[51] could not find a significant association and McGrath et al.[42] concluded a significant increase in offspring BPD risk only in the highest paternal age group (≥45 years). A similar result was noted in other cohorts, where there was only significant in some but not all advanced paternal age (APA) groups (Table 4).[52,53] Similarly, in several case–control studies no robust significant associations could be detected (Table 4).[37,54–56] Lehrer et al.[54] distinguished BPD with and without psychosis. The results of the group without psychosis showed a small protective effect if fathers were of younger age, while a potential protective effect by APA was not significant (Table 4). Chudal et al.[55] noticed a U-shaped relationship with offspring of both younger and older fathers at risk for BPD. Other studies observed no significant results.[37,56] These conflicting results are possibly due to differences in methodology or (lack of) correction for third variables, such as confounding factors or effect modifiers (discussed in section "A new model of causation of mental disorders taking into account paternal age effects").

The impact of offspring's sex and family history of psychosis on the association between APA and BPD was investigated by Laursen et al.,[53] but no interaction was found. In a recent approach by Fountoulakis et al.[57] where bipolar disease outcomes were distinguished by manic or depressive episodes (21 manic cases, 21 depressive cases, 68 controls), a significant risk-enhancing effect was found in all paternal age categories explored (>25, >30, and >40 years) (Table 4). Although this association was

Table 2. Association between paternal age and schizophrenia in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Oldereid et al., 2018	Meta-analysis	Not mentioned (14 studies)	<35 35–39 40–45 45–50 >50	1.06[a] 1.41[a] 1.40[a] 1.40[a] 2.04[a]	1.01–1.12 1.24–1.60 1.27–1.55 1.26–1.56 1.53–2.72	Maternal age
Miller et al., 2011	Meta-analysis	3,011,266	<25 25–29 30–34 35–39 40–44 45–49 ≥50	1.06[a] 1.00 1.06[a] 1.13[a] 1.22[a] 1.21[a] 1.66[a]	1.01–1.11 Reference 1.01–1.10 1.08–1.19 1.14–1.30 1.09–1.34 1.46–1.89	Not mentioned
Wohl and Gorwood, 2007	Meta-analysis	Not mentioned (eight studies)	—	—	—	None
Weiser et al., 2020	Cohort	916,439	16–24 25–29 30–34 35–39 40–44 45–60	0.96 1.00 1.09[a] 1.18[a] 1.29[a] 1.49[a]	0.87–1.06 Reference 1.013–1.18 1.08–1.30 1.14–1.47 1.27–1.75	Year of birth, socioeconomic status, paternal age at birth of the first child, maternal age
Cao et al., 2019	Case control	414 cases, 639 controls	<25 25–29 30–34 ≥35	5.042[a] 5.271[a] 3.728 1.00	1.948–13.046 5.271–12.933 1.401–9.919 Reference	Sex, marriage, age, education, occupation category, character, daily sleep time, living pattern, body mass index
Fountoulakis et al., 2019	Case control	231 cases, 204 controls	>25 >30 >40	2.96[a] 2.80[a] 2.25[a]	1.89–4.60 1.89–4.13 1.04–4.82	Maternal age

[a]Significant at $p < 0.05$.

found for both polarity types of bipolar episodes, results need to be interpreted with some caution given small sample sizes. In conclusion, the available evidence described above suggests a positive association between APA and BPD with variable effect sizes. However, it is still unclear which age could be seen as a perfect "cut-off age" to predict risk for BPD. More and larger studies are needed, and methods to control for confounding factors should be integrated.

Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by obsessions (persistent ideas and thoughts) and compulsions (intrusive and repetitive behavior). Case–control studies by Chudal et al.[58] and Steinhausen et al.[59] could not find a significant association between paternal age and OCD (Table 5). In contrast, Wu et al.[38] found a significant protective effect in fathers aged <25 years and a risk-enhancing effect in fathers aged >30 years, compared to a reference age of 25–29 years. Notably, the latter study had a limited sample size (122 cases, 238 controls) and only a few potential confounders were taken into account, including sex, year of birth, and age of the other parent. Other potential confounders not verified are effects from birth complications and maternal smoking during pregnancy.[60,61] The most recent, and to our knowledge the only, cohort study examining the association between APA and OCD in offspring, dates from 2019 and was performed by Janecka et al.[26] With a large sample size of 1,490,745 subjects, they found a significant protective effect in fathers aged <27.5 years compared to an age of 27.5–32.5 years, but they did not found significant effects by APA (>32.5 years) (Table 5). As was suggested in other disorders (such as ADHD), factors related to the age of the future father may confound true causal relationships. We further discuss this in "Selection into late or early fatherhood and the risk for development of MDs."

Tourette syndrome (TS) is a disorder characterized by multiple motor and vocal tics with variable impact on functioning. No significant paternal age effect has been described.[26,58,62] In a systematic review by Chao et al.,[62] 3 out of 22 studies investigated a potential paternal age effect on TS and no significant association was found. Two other recent studies (one case–control and one cohort study) confirmed this finding,[26,58] while Janecka et al.[26] reported a small but significant risk for TS if the father was <27.5 years old (Table 6).

Notably, evidence for a paternal age effect on *other psychiatric conditions*, such as suicide attempts and substance abuse problems, is almost nonexistent.

In brief, our literature search indicates that paternal age plays an important role in a number of MDs. Although the literature is still scarce, suggested effects of young paternal age are most likely due to a "third variable." However, evidence indicates that the advanced age of men may indeed increase the risk for MDs in offspring, depending on the illness or phenotypes studied. A model to better understand this mechanism is suggested below.

A NEW MODEL OF CAUSATION OF MDS TAKING INTO ACCOUNT PATERNAL AGE EFFECTS

The use of phenotypic characteristics instead of a defined diagnosis

Most research on the etiology of MDs focuses on one exposure or one disorder using the DSM-5 classification. However, it is difficult —if not impossible—to state one specific cause for the development of MDs. In a recent review by de Kluiver et al.,[39] a combination of several risk factors has been proposed, including de novo mutations, epigenetic alterations, environmental factors,

Table 3. Association between paternal age and attention-deficit/hyperactivity disorder in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Janecka et al., 2019	Cohort	1,490,745	<27.5 27.5–32.5 32.5–37.5 >37.5	1.63[a] 1.00 0.84[a] 0.84[a]	1.58–1.68 Reference 0.81–0.87 0.81–0.88	Parity, sex, parental psychiatric history, maternal smoking during pregnancy, gestational age, parental immigration, maternal age
Wang et al., 2019	Cohort	321,272	<20 ≥20	1.27[a] 1.00	1.13–1.42 Reference	Sex, birth year, maternal age, maternal parity, levels of education, self-reported race, median family household income, maternal pre-pregnancy obesity, maternal history of medical comorbidity (one or more diagnoses of the heart, lung, kidney, diabetes, liver disease, cancer), maternal history of psychiatric disorders
Hvolgaard Mikkelsen et al., 2017	Cohort	943,785	≤20 21–25 26–30 31–35 ≥35	2.28[a] 1.49[a] 1.00 0.78[a] 0.61[a]	2.03–2.57 1.40–1.57 Reference 0.74–0.82 0.57–0.65	Gender, parity, birth year, maternal smoking during pregnancy, maternal age
McGrath et al., 2014	Cohort	2,894,688	12–19 20–24 25–29 30–34 35–39 40–44 ≥45	1.44[a] 1.36[a] 1.00 0.96 0.99 1.09 1.32[a]	1.19–1.72 1.27–1.45 Reference 0.91–1.01 0.93–1.06 0.99–1.20 1.16–1.51	Degree of urbanization of place of birth, history of mental illness in a parent/sibling, maternal age, sex, calendar year of birth
D'Onofrio et al., 2014	Cohort	2,615,081	>45	13.13[a]	6.85–25.16	Offspring sex, birth parity, year of birth; maternal age, Swedish nationality (yes/no), education, history of psychiatric hospitalization, history of criminal conviction, paternal income
Cho et al., 2018	Case control	134 cases, 23,427 controls	12–20 21–25 26–30 31–35 30–45	5.05 1.35 1.00 0.69 1.12	0.70–36.17 0.35–5.13 Reference 0.40–1.18 0.55–2.26	Parental level of education, household income, BMI, exposure to environmental smoke at home, adults with depression in household, daily smoking consumption, difference between paternal and maternal age
Chudal et al., 2015	Case control	10,409 cases, 39,125 controls	<20 20–24 25–29 30–34 35–39 40–44 45–49 ≥50	1.55[a] 1.20[a] 1.00 1.03 1.07 1.09 1.26[a] 1.08	1.11–2.18 1.07–1.34 Reference 0.95–1.12 0.97–1.19 0.94–1.26 1.009–1.58 0.73–1.58	Sex, date of birth, place of birth, parental psychiatric history, maternal socioeconomic status, marital status, maternal smoking during pregnancy, number of previous births, birth weight for gestational age, maternal age
St. Sauver et al., 2004	Case control	305 cases, 5326 controls	<20 20–30 >30	1.00 1.72 1.99	Reference 0.62–4.78 0.70–5.65	Sex, parental education levels, race

[a]Significant at $p < 0.05$.

and selection into late fatherhood. This multifactorial approach brings interesting new insights. However, it misses a comprehensive model that can be applied to various conditions and situations; for instance, it primarily focuses on ASD and SCZ. We believe that a more holistic point of view is needed, like the one adopted by the National Institute of Mental Health of the United States in their Research Domain Criteria (RDoC) initiative. RDoC is a research framework for investigating MDs. It integrates many levels of information (from genomics and circuits to behavior and self-report) to explore basic dimensions of functioning that span the full range of human behavior from normal to abnormal.[63]

Based on our interpretation of the reports discussed above and here below, we believe that the paternal age effect together with other determinants acquired in (or before) life plays an important role in the development of a MD. Next, defining the phenotypic features rather than a predetermined diagnosis may be more useful for future treatment and research in this field. For instance, Lehrer et al.[54] investigated the paternal age effect in SCZ and BPD with and without psychotic features, using a 90-item Operational Criteria Checklist for Psychotic Illness. They found a positive association between APA and SCZ or BPD if patients showed psychotic features, but not if these psychotic features were not manifested. This suggests that the effect of APA is psychosis, rather than other aspects of these disorders. The authors indicate that APA may be part of a complex underlying mechanism. This finding may have important clinical applications as APA-related patients may benefit from a personalized treatment plan. At least two studies have shown that paternal age-related SCZ patients showed a better response to treatment with drugs like dopamine antagonists[64] or other antipsychotics such as paliperidone,[65] compared to patients born from younger fathers. Next, a population-based study including questions on psychosis (but

Table 4. Association between paternal age and bipolar disorder in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Weiser et al., 2020	Cohort	916,439	16–24 25–29 30–34 35–39 40–44 45–60	0.86 1.00 0.97 1.06 1.01 1.21	0.68–1.10 Reference 0.79–1.19 0.79–1.43 0.66–1.55 0.70–2.11	Year of birth, socioeconomic status, paternal age at birth of the first child, maternal age
Byars and Boomsma, 2016	Cohort	1,743,269	16–20 21–25 26–30 31–34 35–39 40–44 45–60	1.4421 1.0071 0.9404 1.00 1.1567 0.9383 0.9433	0.6243–3.3309 0.6621–1.5317 0.7219–1.2250 Reference 0.8647–1.5474 0.5613–1.5683 0.4160–2.1387	Maternal age, maternal pre-existing conditions (pre-existing hypertension, pre-existing diabetes, previous spontaneous or induced abortions), maternal pregnancy-related or induced variables (gestation length, gestational diabetes, gestational hypertension, bleeding, fetal oxygen deprivation, pregnancy edema), parental variables (psychiatric diagnosis, years of education, average income), birth-related variables (birth weight, birth season, birth year, Apgar 5 score), child-related variables (sex, nationality, demographic parity, region)
McGrath et al., 2014	Cohort	2,894,688	12–19 20–24 25–29 30–34 35–39 40–44 ≥45	1.19 1.04 1.00 1.06 1.06 1.03 1.24[a]	0.99–1.40 0.97–1.12 Reference 0.99–1.13 0.97–1.16 0.90–1.17 1.05–1.45	Degree of urbanization of place of birth, history of mental illness in a parent/sibling, maternal age, sex, calendar year of birth
Menezes et al., 2010	Cohort	711,989	<21 21–24 25–29 30–34 35–39 40–44 45–49 ≥50	1.35 1.00 1.15 1.41 1.68[a] 1.85[a] 1.06 1.43	0.67–2.75 Reference 0.83–1.59 0.99–2.00 1.09–2.61 1.04–3.30 0.39–2.83 0.43–4.76	Gender, date of birth, place of birth, obstetric characteristics (season of birth, gestational age, birth weight, Apgar score, maternal parity, singleton or multiple birth), family history of psychosis and BPAD, death of a parent before the age of 15 years, childhood socioeconomic position (annual income, socioeconomic status, education), maternal age
Laursen et al., 2007	Cohort	>2,100,000	≤20 21–25 26–30 31–35 36–40 41–45 46–50 51–55 ≥56	0.89 1.00 1.08 1.21[a] 1.21[a] 1.14 1.26 1.71[a] 1.03	0.75–1.07 Reference 0.98–1.18 1.09–1.34 1.09–1.42 0.96–1.36 0.99–1.61 1.21–2.41 0.53–2.01	Age, calendar time, gender, family history of psychiatric admission, loss of parent, place of birth, maternal age
Fountoulakis et al., 2019	Case control	21 manic cases, 21 depressive cases, 204 controls	Manic cases: >25 >30 >40 Depressive cases: >25 >30 >40	12.35[a] 5.62[a] 4.56[a] 3.71[a] 2.34 6.06[a]	1.63–94.09 1.97–15.96 1.29–16.11 1.06–13.02 0.94–5.82 1.84–19.89	Age, gender, diagnosis
Lehrer et al., 2016	Case control	434 cases, 7658 controls	<20 20–24 25–29 30–34 35–39 40–44 ≥45	0.440[a] 1.00 0.879 0.795 0.988 0.920 0.934	0.220–0.798 Reference 0.660–1.174 0.587–1.077 0.718–1.359 0.593–1.391 0.536–1.543	Difference between paternal and maternal ages, sex, race
Chudal et al., 2014	Case control	1861 cases, 3643 controls	<20 20–24 25–29 30–34 35–39 40–44 45–49 ≥50	0.90 1.35[a] 1.11 1.00 1.02 1.27 1.28 2.84[a]	0.48–1.69 1.06–1.72 0.94–1.31 Reference 0.84–1.25 0.94–1.73 0.75–2.17 1.32–6.12	Parental psychiatric history, educational level, place of birth, maternal age
Brown et al., 2013	Case control	94 cases, 746 controls	15–24 25–34 35–44 ≥45	1.16 1.00 1.25 1.45	0.57–2.34 Reference 0.67–2.31 0.51–4.11	Parental education, parental ethnicity, maternal age, gestational age
Buizer-Voskamp et al., 2011	Case control	1121 cases, 4484 controls	<20 20–24 25–29 30–34 35–39 ≥40	1.68 0.82 1.00 1.12 0.99 1.14	0.94–3.01 0.65–1.03 Reference 0.96–1.32 0.80–1.22 0.84–1.55	Social economic status, ethnic background, maternal age
Frans et al., 2008	Case control	13,428 cases, 67,140 controls	<20 20–24 25–29 30–34 35–39 40–44 45–49 50–54 ≥55	1.12 1.00 1.04 1.11[a] 1.09[a] 1.15[a] 1.14[a] 1.21[a] 1.37[a]	0.94–1.34 Reference 0.97–1.11 1.02–1.19 1.00–1.19 1.04–1.28 1.00–1.30 1.00–1.48 1.02–1.84	Parity, socioeconomic status, family history of psychotic disorders, maternal age

[a]Significant at $p < 0.05$.

Table 5. Association between paternal age and obsessive-compulsive disorder in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Janecka et al., 2019	Cohort	1,490,745	<27.5 27.5–32.5 32.5–37.5 >37.5	0.90[a] 1.00 1.02 1.08	0.84–0.96 Reference 0.95–1.10 0.99–1.18	Parity, sex, parental psychiatric history, maternal smoking during pregnancy, gestational age, parental immigration, maternal age
Chudal et al., 2017	Case control	1358 cases, 5381 controls	<19 20–24 25–29 30–34 35–39 40–44 45–49 ≥50	0.90 0.91 1.00 0.95 1.10 1.14 1.45 1.29	0.38–2.13 0.69–1.19 Reference 0.79–1.13 0.89–1.37 0.85–1.54 0.91–2.31 0.66–2.53	Age of the other parent, paternal and maternal psychiatric history, maternal socioeconomic status, maternal smoking during pregnancy, parity, birth weight for gestational age, marital status
Steinhausen et al., 2013	Case control	2057 cases, 6055 controls	13–35 35–67	1.00 1.11	Reference 0.97–1.27	Sex, year of birth, month of birth, degree of urbanization
Wu et al., 2012	Case control	122 cases, 238 controls	<25 25–29 30–34 ≥35	0.289[a] 1.00 2.225[a] 5.413[a]	0.105–0.800 Reference 1.266–3.909 2.154–13.602	Sex, year of birth, age of the other parent

[a]Significant at $p < 0.05$.

Table 6. Association between paternal age and Tourette syndrome in offspring.

Authors	Study design	Number of subjects	Categories of paternal age (years)	Odds ratio	95% Confidence interval	Adjusted for confounding factors
Janecka et al., 2019	Cohort	1,490,745	<27.5 27.5–32.5 32.5–37.5 >37.5	1.09[a] 1.00 0.99 1.00	1.01–1.18 Reference 0.91–1.06 0.91–1.10	Parity, sex, parental psychiatric history, maternal smoking during pregnancy, gestational age, parental immigration, maternal age
Chudal et al., 2017	Case control	1195 cases, 4538 controls	<19 20–24 25–29 30–34 35–39 40–44 45–49 ≥50	1.80 0.90 1.00 1.07 0.93 0.99 1.20 1.13	0.86–3.78 0.69–1.17 Reference 0.89–1.29 0.73–1.18 0.72–1.39 0.71–2.01 0.53–2.42	Age of the other parent, paternal and maternal psychiatric history, maternal socioeconomic status, maternal smoking during pregnancy, parity, birth weight for gestational age, marital status

[a]Significant at $p < 0.05$.

not a predefined disease, according to DSM-5) showed that respondents whose fathers were aged >35 years at the time of their birth had 2.12 times higher odds of psychotic-like symptoms (95% CI: 1.08–4.16), compared to offspring from fathers aged between 25 to 29 years at birth. Note, there was no relationship between maternal age and psychotic-like symptoms.[66]

Realizing that a treatment plan, as well as the etiology and development of aberrant behavioral or mental traits of an individual, may differ by case, a determined diagnosis as classified in the DSM-5 may not always offer the solution expected. Below we suggest and explain a multifactorial and holistic explanatory approach including a number of mechanisms contributing to a patient's specific symptomatology or final diagnosis (Fig. 1). This hypothesis is part of the Paternal Origins of Health and Disease (POHaD) paradigm suggesting the role of the father in the disease development of children through his exposures throughout life or other male-related factors.[67,68] Our suggested model may serve as a blueprint for future research designs, to help inform patients and health-care workers raising the awareness and/or organizing preventive care and optimal guidance for patients and their family.

The role of de novo mutations and genetics in the origin of MDs

Current developments in biotechnology and genome-wide association studies facilitate the understanding of genetic aspects of MDs. Hundreds of genes and associated single-nucleotide polymorphisms (SNPs) have been linked to ASD, SCZ, and ADHD phenotypes.[69–71] No single gene or SNP makes a major contribution to any of these disorders. Most likely a combination of genetic aberrancies codetermines the occurrence and the degree of the disorder.[69] In addition, deletion or duplication of copy number variants (CNVs) has been related to SCZ. For instance, deletions at chromosome 1q21.1, 15q11.2, and 15q13.3 have been correlated to SCZ and related psychosis.[72] While a specific disorder may run in a family, de novo CNVs and SNPs at gene locations involved in disorder development have been found in children from families without a history of MDs.[73] This "de novo mutation" hypothesis has become a widely accepted theory explaining the origin of new and unexplained diagnoses of MDs.[74,75] This is particularly the case in ASD and SCZ, as well as in extremely rare occasions of genetic neurodevelopmental disorders, such as KAT6A syndrome.[76] Wilfert et al.[77] presented a comprehensive overview of the most important known de novo

mutations in MDs, including large CNVs, small indel mutations, missense mutations, and single-nucleotide variants. These mutations particularly occur in gene networks and anatomic regions important in neuronal development and genesis of MDs. For example, in ASD, mutations occur in genes for cell proliferation, neuronal migration, and synaptic networks, located in cortical and striatum neurons.[77,78] O'Roak et al.[78] estimated that between 384 and 821 different loci are important in ASD, with some overlap with other disorders, including intellectual disability and delay in development. This overlap could be explained by the common pathophysiology and anatomic origins of these disorders.[79]

It has been demonstrated that most of the de novo mutations in children are of paternal origin. As in the somatic mutation theory of aging,[80] the genome of germ cells are also susceptible to age-related modifications.[81] Consequently, older parents may transmit their acquired de novo mutations to their offspring. A substantial number of MDs, including ASD, SCZ, and intellectual disability have been found to be caused by paternal genetic changes.[82] In some cases, such pathogenic mutations have been traced two generations back, suggesting a transgenerational effect in some disorders, that is, SCZ and ASD.[83] Through a genome-wide sequencing study by Kong et al.[84] where 78 parent–offspring trios (44 ASD, 21 SCZ, and 13 others) have been compared, an average of 14.2 and 55.4 de novo SNPs originated from the mother or the father, respectively. Moreover, the number of mutations in the offspring increased with paternal age (~2 mutations per year), while maternal age did not show a significant effect. The difference in frequency of de novo mutations by parental origin could be explained by the fact that the male germline is more susceptible to mutations than the female germline. Before puberty, primordial germ cells develop to spermatogonia. In each reproductive cycle, cells further replicate, and finally mature spermatozoa are formed. These replication rounds (throughout life) increase the risk of integrated errors in DNA code of sperm. Because female germ cells replicate before birth, their risk to acquire de novo mutations is lower, but still apparent. To illustrate, in the above-mentioned systematic review of Wu et al.[22] concerning ASD, the risk was 41% higher in the highest maternal age category compared to the reference age, in contrast to a 55% risk increase in the highest paternal age category. This difference could be explained by the higher mutation burden in fathers compared to mothers.

The importance of germline-induced diseases has also been explained by the so-called "selfish spermatogonial selection."[26,85] This theory explains how a specific change in the genetic code may result in a detrimental effect. For instance, male adult stem cells with mutations at loci important in growth and proliferation (e.g., tyrosine kinase-Ras-MAPK pathways) can expand clonally.[85] This phenomenon leads to an overweight of mutated sperm cells in comparison with non-mutated sperm cells. If these mutations are also pathogenic for an MD, or if these mutated stem cells carry other mutations, which in turn are pathogenic for an MD, then this results in an exacerbation of the effect of the pathogenic de novo mutation. For example, Goriely et al.[85] noticed that there is an overlap between the molecular pathways linked to spermatogonial selection and those linked to SCZ and ASD. If the resulting phenotype allows reproduction, this could also be an explanation for the transgenerational effect of some disorders.

Nevertheless, the de novo mutation theory should be interpreted with caution. While it was once a leading hypothesis, recent literature shows some contradicting results. First, some studies also observed an increased SCZ risk in offspring of younger parents, as illustrated in Table 1 by the results of Miller et al.,[34] Cao et al.,[35] and Oldereid et al.[86] These findings cannot be reconciled with a theory that SCZ is solely caused by mutations that accumulate with father's age. Second, several authors found that age at first childbirth is more important than the age at birth of any child later in life.[87,88] Third, it is known that some of the MDs are associated with sub- or infertility, which is another possible argument against the sole role of mutations in the intergenerational effect of disorders.[89]

None of the above-mentioned arguments are sufficiently strong to completely reject the de novo mutation theory. Some critical insights suggest that the contribution of APA-related de novo mutations to the risk of developing an MD in offspring is not >10–20% of the total risk increase by paternal age.[90] According to Gratten et al.,[90] spermatogonial selection plays a relatively unimportant role in the paternal age effect of MDs, compared to the paternal age at first childbirth. The latter refers to the "selection into late fatherhood hypothesis," which will be discussed below. Similar suggestions and conclusions were discussed by Taylor et al.,[82] who investigated whether the rate of de novo mutations could account for the epidemiological findings in five disorders, including ASD and SCZ. Through whole-genome sequencing data of parent–offspring trios, they designed several genetic models to predict the offspring risk of SCZ and ASD, in relation to paternal originating de novo mutations. These predictions were compared to epidemiologic findings in a Danish national population-based cohort. Like that, they hypothesized that de novo mutations only make a small contribution to the paternal age effect in these disorders. Next to de novo genetic alterations in sperm, age also causes a functional decline of DNA repair mechanisms and inadequate antioxidant responses or increased levels of reactive oxygen species (ROS). This combination of factors increases the risk for accumulation of the number of mutations or to affect the sperm epigenome (see below). The risk of transmitting novel genetic defects to the offspring thus increases.[37]

The role of epigenetics in the development of MDs

A new concept of the contribution of paternal age to the development of MDs is the "epigenetic hypothesis."[91,92] Epigenetic mechanisms include DNA methylation, histone modifications, and transcription of noncoding RNAs. Alterations thereof influence gene expression, regardless of the genomic code. The epigenetic system is important in tissue-specific regulation of gene expression, genomic imprinting, and cellular regulation. However, aging causes changes in the sperm epigenome. Jenkins et al.[93] observed an age-related global hypermethylation, gene-specific hypomethylation, and alteration of the expression of the enzymes responsible for these methylation processes in sperm cells. Unfortunately, few men were tested ($n = 17$). This study limitation makes it difficult to exclude influences from long-term environmental exposures (as will be discussed below). The epigenetic changes detected in sperm cells were in contrast with the age-related methylation patterns found in somatic cells by others, including global hypomethylation and gene-specific hypermethylation.[94] Furthermore, the presence and modification of histone proteins and their responsible enzymes also alter with aging in a variety of cells.[94] Although still hypothetical, if inherited, age-related epigenetic alterations in sperm cells could lead to different gene expression, potentially influencing neurodevelopment and behavior in offspring. However, inheritance of DNA methylation patterns, for instance, acquainted by a former generation can only be explained if the affected regions withstand reprogramming in the zygote. As imprinted genes are able to overcome this epigenetic programming process their methylated or unmethylated status at specific gene regulatory sites may serve as a signature of paternally acquired exposures.[95] In this context, we earlier found an association between paternal obesity and aberrant methylation patterns in offspring at birth;[96,97] but effects from age on imprinted or other potential site remain an underexplored area of research. A study by Feinberg et al.[98] investigated the association between DNA methylation in paternal sperm and autism phenotype in an autism-enriched cohort. They found that differentially methylated regions (DMRs) in sperm DNA

had different methylation patterns if infants showed a strong indication to develop ASD in their first year of life, compared to sperm DMRs from fathers of children who were found to be negative for these specific assessments (i.e., performance on the Autism Observational Scale for Infants). While the approach by Feinberg et al.,[98] using a selected cohort, has its limitations, it help to identify important epigenetic players.[68] For instance, methylation alterations were located at genes important in neurogenesis, such as *SNORD115-15* and *SMYD3*.

An animal study comparing DNA methylation patterns in sperm between young and old mice, partly confirmed this epigenetic hypothesis.[92] While no global methylation differences were found, local hypomethylation at regions important for regulation of gene transcription was measured in sperm from older mice. In addition, regulatory gene sites were also hypomethylated in the brain from offspring. Most significant results were found at *En2*, *Cbln1*, and *NeuroD1* genes. Furthermore, a comparison in offspring behavior between mice from young and old fathers showed reduced startle and exploratory behavior and a weaker prepulse inhibition if fathers were older. This behavior is comparable to human behavior in SCZ and ASD.[92]

Denomme et al.[99] recently investigated the impact of APA on placental imprinting in mice. They found a significant hypermethylation of DNA at the *Kcnq1ot1* imprinting control region of placentas if mice were fertilized by males at the age of 11–15 months versus (the same) males at the age of 4–6 months. Human evidence for a paternal age effect on imprinting is lacking. However, we recently found a link between APA and suboptimal embryo growth, a phase of development where imprinted genes play an important role.[100]

Epigenetic alterations can also be caused by environmental factors such as air pollutants, lifestyle factors, nutrition, intake of medication, and chemotherapy, or a combination thereof, known as the *paternal exposome* or the totality of exposures.[68,94,101] This can occur throughout life but also in fathers before conception. This concept of environment-related epigenetic alterations passed on to future generations has been defined earlier through the POHaD hypothesis, or the overarching Developmental Origins of Health and Disease theory.[68] Hence, we believe that father–offspring effects should be taken into account when interpreting studies on MDs. For example, an epigenetic alteration found in offspring of an older father, and associated with SCZ, could also be caused by chronic exposure to certain environmental factors, including chronic use of antipsychotic medication. This indicates the importance of future research and assessment of intergenerational effects of the use of drugs in men (and women) before having a child. Furthermore, the timing of the paternal exposure (to medication and/or other potential determinants) should be integrated into future studies related to this father–child inheritance of phenotypes. At least four windows of susceptibility wherein environmental influences can alter the epigenetic profile of male germ cells have been suggested to play a role in this process of inheritance.[15]

Notably, epigenetic changes may in turn alter fertility, causing a delay in onset of childbearing, which increases the risk for MDs (as discussed below in "Selection into late or early fatherhood and the risk for development of MDs").

We further hypothesize that with aging, the ability to reprogram the epigenome of sperm cells may decline, and epigenetic alterations (both age-related and exposure-related) could pass easily through to the next generation.[15]

Important to keep in mind is the probable two-way dialog between genetics and epigenetics: (i) epigenetic alterations could influence genomic stability and lead to more de novo mutations, possibly inducing spermatogonial selection. Also, (ii) genetic polymorphisms and/or mutations could influence susceptibility to epigenetic alterations, either age-related or exposure-related.[14] Notably, it is possible that not "age" is the main reason for disease development, but the accompanied accumulation of errors in the sperm epigenome by environmental exposures throughout life. These trains of thought need to be further examined in future research.

Selection into late or early fatherhood and the risk for development of MDs

Literature suggests that a "selection into late fatherhood" contributes to an increased risk of MDs in offspring.[87] This means that combined factors leading to advanced age at first childbearing in the father also predispose the offspring to MDs. For instance, ASD and SCZ are related to a decreased fecundity.[89] Hence, the advanced age at childbearing is directly linked to a transmission of a father's disorder to his children, if the origin of subfertility is a heritable one. As behavioral and social skills are often diminished in patients with MDs, difficulties to start and build a relationship may also delay fatherhood. On some occasions, the father may not overtly show symptoms of the condition, but he may pass a genetic vulnerability onto his children. For as yet unknown reasons, his children may develop an overt MD. If this potential cause of disease is overlooked, and fathers are not questioned in the clinic or included in a study, this "hidden" paternal genetic risk factor is a missed link in defining the etiology of MDs. If the "paternal history of a MD" (or "paternal MD") is known, some studies corrected for this factor as a potential confounder. However, in some cases, this approach may not be optimal. The association between the third variable (an underlying "paternal MD") and "having a child with an MD" may be dependent on the age of the father (the exposure of interest); for example, if APA and a genetic underlying factor of the father have a multiplicative effect. In this case, the underlying third factor is not a confounder, but an effect modifier. Consequently, a stratified analysis is needed. More specifically, strata of healthy fathers and fathers with a MD should be analyzed separately by age of the father. In each of these strata, one could then calculate the OR for having a child with a MD if the father was <25 years old versus a reference age of 25–35 years old (for instance); the same could be done for fathers >35 years old versus a reference group. This approach would help estimate the unbiased effects of paternal age in each subgroup. Another important determinant to keep in mind is the role of the mother. Women who choose an older partner could have some personality or behavior characteristics that predispose their children to MDs.[83] For example, Miller et al.[102] demonstrated a positive association between maternal SCZ and APA, suggesting that the paternal age effect of psychosis in offspring can be explained by an increased genetic risk from the mother.

Alternatively, as already suggested above, "selection into early fatherhood" has also been suggested in some reports. Frans et al.[74] showed that men diagnosed with SCZ, BPD, or ASD had children at a younger age, compared to healthy men. Affected men were even more likely of becoming a father at a very young age (as a teenager). The authors suggested that not only the paternal disorder should be studied (as a third variable or a reason for young fatherhood) but also related familial factors need to be taken into account, such as underlying sociodemographic factors. Young men affected with a psychiatric disorder may also be more prone to deviate from social and reproductive norms, as was already suggested above in the context of ADHD.

Convincing evidence regarding the role of "selection into early or late fatherhood" comes from epidemiological studies focusing on paternal age of first childbearing. As noted, Gratten et al.[90] found a correlation between paternal age at first childbirth and vulnerability to psychiatric disorders. Several authors demonstrated a disappearance of the paternal age effect on ND in offspring after correction for age at first parenthood.[37,87,88] They suggest that the earlier measured associations between APA and an MD could be masked by a confounding factor, namely, a

delayed (or earlier) age at first fatherhood because of an underlying inheritable condition. However, as we suggested above these analyses need a stratified approach.

Notably, Puleo et al.[103] investigated whether autism-related personality traits such as rigidity, hypersensitivity, anxiousness, and aloofness were associated with advanced age at childbearing in an autism-enriched cohort of 131 parent–child dyads. While the study sample was small and narrow (autism-enriched), and assessments were self-reported, no significant associations were found between paternal age at first childbirth and paternal autism personality traits.[103] If these results are reproducible in a larger cohort, they contradict the "selection into late fatherhood" and suggest that earlier measured associations between APA and autism may not be affected by paternal behavioral traits.

Furthermore, correction for all possible confounding factors is of the utmost importance to unravel the underlying mechanisms of the association between APA and MDs. For example, the use of assisted reproductive techniques (ART) not explained in this review could be an important (and often unmeasured) confounder. After all, the use of ART is more common in older fathers than in younger fathers, and may lead to epigenetic changes in the zygote that can contribute to the development of MDs.[104] Next, one has to keep in mind that when a factor appears in the causal pathway between APA and an ND in offspring, correction for this factor will attenuate the association.[26] Similarly, if maternal age or the presence of a maternal psychiatric history is a contributor to the development of MDs in offspring, correction for this cofactor will decrease the association found.

Environmental resources and development of MDs

The fourth contribution to the paternal age effect of MDs is the "environmental resource" or the "psychosocial" hypothesis.[105] Older men live in a different socioeconomic environment than younger men. There may be differences in educational background, psychological, economical, medical, and behavioral aspects. Differences in the environment can be protective or risk-enhancing. It has been demonstrated that children of advanced age parents have a more stable and supportive home situation with adult parenting behavior, less risk behavior such as smoking and drinking, a stable financial situation, and good access to health care and education.[42] On the other hand, older parents can have an isolated social life, possibly leading to decreased social skills and explorative behavior in offspring. However, care should be taken when generalizing these characteristics. Nilsen et al.[105] observed in a Norwegian population study ($n = 14\ 832$) that the subgroup of older fathers was heterogeneous with regard to sociodemographic characteristics. While most men had a stable home situation, a significant number consumed alcohol, were overweight, or experienced a less stable socioeconomic situation. Older men had more physical and mental health problems (such as cardiovascular diseases and depression).[105] Babadagi et al.[106] investigated the impact of temperament, rearing, character, and psychopathology of the father on the temperament of his child (with a mean age of 53 months) in 200 couples. A large number of exposures (characteristics of the father) and outcomes (temperament of the child) were examined through questionnaires. Their results showed a complex interplay between paternal and offspring personality. For example, fathers who avoided harm strongly had children who expressed more fear, shyness, and impulsivity. Authoritarian fathers had children with more fear and less smiling or laughing. Fathers with OCD or phobic anxiety had children with more anger and disappointment.[106] These are just a few of their observations, as an illustration of a complex interplay between psychosocial environment and offspring personality development, whether or not it is pathological.

Because of the few literatures on the relationship between psychosocial environments of APA and MDs in offspring, firm conclusions cannot be drawn.

Implementation of our APA-based model

Impact on future clinical applications. Current knowledge suggests that paternal age plays an important role in the development of MDs, but a clear association and interaction analyses are needed between multiple cofactors to decipher its role and those of other players. Moreover, a one exposure-one disease theory (or *specificity*), as was originally suggested by one of the Bradford Hill guidelines for a causal relationship between exposure and outcome, is generally not valid in modern epidemiology.[107] We here combine currently used theories and propose a multifactorial model in which paternal influences, advancements in (epi)genetic insights, and knowledge on the complexity of social and other components are integrated. This model, presented in Fig. 1, can be used as a tool to further decipher the impact of each component as a potential cause of the disorder in a particular situation, subpopulation, or individual. In addition to the identification of attributed effects of specific exposures, our model could help identify a potentially "proximate" cause, implying a direct or major responsibility of the disease of interest.[108] Importantly, treatment plans should benefit if the attributed proportions of these determinants are included in the process of designing a more personalized care for patients experiencing psychological or behavioral problems.

It should be noted that these risk factor components are not mutually exclusive and most likely interact in a context-specific way. For example, a de novo mutation can have the ability to induce an MD, but the final result, that is, the ultimate extent of this disorder in offspring, will depend on other factors acting in concert, such as epigenetic status, environmental factors throughout life, education, comorbidities, and so on. On the contrary, while some children may be genetically predisposed, effective (intended or unintended) prevention through supportive surroundings, such as family support, education, and adequate follow-up, may result in absence of the disorder. In some cases, if these interactions are better understood, patients may ultimately need fewer prescription drugs to treat their condition.

Impact on future research. Epidemiological studies clearly show that paternal age directly or indirectly contributes to the development of ASD and SCZ. However, in BPD evidence about an effect from APA is less robust, but emerging. In ADHD, APA seems to have a protective effect. In OCD and TS, there is insufficient research to draw firm conclusions. Our multifactorial model may contribute to a better understanding of underlying interactions with other disease determinants and the interplay between genetics and environment; this fills the current knowledge gaps in the development of MDs. However, more research is needed to explore our hypothesis. An as yet unknown fact is the weight of the role of the father in the development of an MD, compared to other causal components. This may even differ by the outcome measured, such as "age at onset," "severity," or "response to treatment" of the disorder.[65,109] These considerations are important directions for future research and translation to clinical applications.

While it has been suggested that aging gradually increases the risk for MDs in offspring,[17] it would be useful to define a cut-off age for clinical practice. Most studies discussed here used 25–29 years as a reference age, whereas few used 30–34 years as a cut-off. While there is currently no universally accepted definition of APA, other studies where various risk factors have been studied defined a cut-off age of 40. This was based on infertility issues, failure when implementing ART, miscarriage, birth defects, childhood cancer, and neurodevelopment disorders.[19,110]

It is of utmost importance that future research brings the emphasis on a comprehensive and multifactorial approach. This is necessary to unravel the causal interactions and underlying mechanisms of the paternal age effect. Our multifactorial model can serve as a guide for epidemiologists to interpret population-

based data from large cohorts, to avoid bias and confounding, and above all, to investigate the causal pathways and causal relationships. Furthermore, fundamental researchers should seek new (epi)genetic insights, providing more understanding of the underlying biological explanatory mechanisms of these MDs, thus providing handles for further epidemiologic research. With techniques such as artificial intelligence and machine learning large amounts of data could be interpreted, facilitating further understanding of diseases and associations with contributing and confounding factors. Thus, research should be a dynamic interaction and cooperation between epidemiologic researchers, clinicians, and fundamental researchers, to identify knowledge gaps and seek effective strategies to solve them. The ultimate goal is to unravel the exact mechanisms of the paternal age effect and discover the disease-, context-, and individual-specific manner of interaction between the different contributors, in order to apply this new knowledge to practice preventive and therapeutic strategies.

Impact on public health and prevention

Our multifactorial model can help raise awareness for both MDs in children and the impact of delaying parenthood. Moreover, it can serve as a base for education, guidance, and support programs for parents pre- and post birth. For example, giving information on the possible impact of delaying parenthood, both protective and risk-enhancing aspects, as well as offering help or guidance in educating children. Another aspect for which the multifactorial model can serve as a guide is as a screening and/or treatment plan, which should be organized in a multidisciplinary way and should focus on all possible contributors of an APA-related disease.

CONCLUSIONS

Current literature on the causation of MDs in children is somewhat dispersed. Single risk factors and tentative models combining these factors have been proposed, but these hypothetical models do not include all known aspects or biological findings that have been established over the last few years. Lack of a holistic explanatory model limits development of optimal treatment strategies. One new aspect of the latest developments on the etiology of offspring diseases is the role of the father. We, therefore, studied the association between APA and MDs in offspring and developed a new comprehensive model of causation, integrating the latest findings from the literature. This is consistent with Rothman's theorem: "as layers of confounding are left behind, we gradually approach a deeper causal understanding of the underlying biological processes."[111] Our model could be used as a basis to study the etiology of MDs through epidemiological research and/or animal modeling. In the following step, it could be applied in pediatric clinical practice in tailor-made therapy plans, serving as a guide for providing advice and therapy to patients, as well as for public health recommendations.

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AUTHOR CONTRIBUTIONS

I.V. developed the conception and design of this review, acquired the data, and wrote the interpretation to draft the manuscript, C.D. wrote the clinical aspects and relevance of this work and the interpretation of the study designs used. A.S. is the principal investigator who oversaw the conception and design of this review, and who contributed to the discussion and editing of the final manuscript. All authors have read and approved the final version of the manuscript and given their approval of submission for publication.

ADDITIONAL INFORMATION

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