



## The association between the presence of genetic disease in the offspring and the paternal age: A systematic review

### La asociación entre la presencia de enfermedad genética en la descendencia y la edad paterna: una revisión sistemática

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#### Abstract

**Objective:** To determine the association between the presence of genetic disease in the offspring and the paternal age.

**Methods:** We carried out a systematic review in: Medline (Ovid), EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), from encompassing the full catalogue up until October 2022. We included RCTs, Cohort, case-control and cross-sectional studies. Every study was evaluated according to eligibility criteria. Meta-analysis was not possible given the clinical and methodological heterogeneity.

**Results:** We identified 502 studies through the database search. Forty-five studies were selected for data collection and were included in the qualitative analysis. In this systematic review we did not find associations with anomalies such as Trisomy 18, Obsessive Compulsive Disorder, Tourette syndrome, schizoaffective disorder, adverse perinatal outcomes, hematologic disturbances, microcephaly, hydrocephalus, gastrointestinal disturbances, cleft lip with or without cleft palate, cleft palate, and genitourinary disturbances. In contrast, we found a tendency of association between older fathers and psychiatric disorders (schizophrenia, autism, bipolar disorder syndrome, intellectual disability), nervous system cancer and overall musculoskeletal congenital anomalies.

**Conclusion:** There is a tendency of association among the advanced paternal age and an increased number of birth defects regarding some specific conditions.

#### Keywords:

Paternal aging,  
genetic diseases,  
advanced paternal age,  
systematic review

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## Resumen

**Objetivo:** Determinar la asociación entre la presencia de enfermedad genética en la descendencia y la edad paterna.

**Métodos:** Realizamos una revisión sistemática en: Medline (Ovid), EMBASE, *The Cochrane Central Register of Controlled Trials* (CENTRAL), desde el inicio hasta octubre de 2022. Incluimos ECA, estudios de cohortes, de casos y controles y transversales. Cada estudio fue evaluado de acuerdo con los criterios de elegibilidad. El metaanálisis no fue posible dada la heterogeneidad clínica y metodológica.

**Resultados:** Identificamos 502 estudios a través de la búsqueda en la base de datos. Se seleccionaron cuarenta y cinco estudios para la recopilación de datos y se incluyeron en el análisis cualitativo. En esta revisión sistemática no encontramos asociaciones con anomalías como trisomía 18, trastorno obsesivo compulsivo, síndrome de Tourette, trastorno esquizoafectivo, resultados perinatales adversos, alteraciones hematológicas, microcefalia, hidrocefalia, alteraciones gastrointestinales, labio hendido con o sin paladar hendido, paladar hendido y trastornos genitourinarios. Por el contrario, encontramos una tendencia de asociación entre padres mayores y trastornos psiquiátricos (esquizofrenia, autismo, síndrome de trastorno bipolar, discapacidad intelectual), cáncer del sistema nervioso y anomalías congénitas musculoesqueléticas en general.

**Conclusión:** Existe una tendencia de asociación entre la edad paterna avanzada y un mayor número de malformaciones congénitas respecto a algunas condiciones específicas.

### Palabras clave:

Envejecimiento paterno, enfermedades genéticas, edad paterna avanzada, revisión sistemática

## Introduction

According to the National Human Genome Research Institute, *a genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence*. The same Institute states that genetic disorders are very wide, and it encompasses disorders caused by mutations in one isolated gene (monogenic disorders), multiple genes (multifactorial inheritance disorder), damage to chromosomes with a consequent change in number or structure of them, and even the combination of genes mutations and external environmental factors. The effects

of these genetic disorders range from pregnancy loss to developmental, physical, and mental alterations, not to mention the social, economic, and healthcare burden they represent.

As almost all conditions have a genetic component; it is remarkably important to elucidate as many risk factors as possible to be able to prevent them.

Nowadays, given the tremendous changes in health, social, and most of all, cultural scenarios, delaying childbearing has become a widespread phenomenon, mainly among de-

veloped countries.<sup>(1-3)</sup> Postponing pregnancy comes with several consequences, especially for the offspring.

The negative impact of advanced maternal age on reproductive outcomes has been widely studied and is well documented. It has been linked to decrease in fertility rates, increase in miscarriage rates, pregnancy complications, congenital anomalies, and perinatal mortality.<sup>(1,4,5)</sup>

Just as maternal age is of concern, paternal age, independently from the former, should also be a topic of interest. Even if it is still not as clear, advanced paternal age has an important correlation to negative outcomes both for the pregnancy, and for the newborn.<sup>(6-9)</sup>

Some evidence points out a negative effect of father aging on embryo development beyond the cleavage stage. Besides, advanced paternal age correlates with an increased risk of pregnancy loss, and newborn disorders such as monogenic diseases, autosomal dominant diseases, neuropsychiatric and neurocognitive disorders, and even augmented cancer risk.<sup>(6,10)</sup> Most of the available studies are retrospective, and there is a considerable heterogeneity among them. The principal issue being that not even an age threshold has been established yet. Some propose >34 years, others >40 years, others >45 years, and so on.<sup>(6)</sup>

It is mandatory to elucidate the exact consequences of paternal advanced age on pregnancy and the offspring, mainly for couple counseling regarding postponing childbearing.<sup>(1)</sup> Then, we aimed to determine the association of specific outcomes in the offspring and the paternal age.

## Methods

We conducted this study according to the Cochrane collaboration recommendation and following the PRISMA statement. PROSPERO registration number CRD42018118197.

## Eligibility criteria

**Study designs:** RCTs, Cohort, case-control and cross sectional studies, in whom association between advanced paternal age and genetic diseases in the offspring

**Participants:** Studies including men  $\geq 18$  years-old and their association with the presence of offspring inherited genetic diseases.

**Factor:** Age (Increasing age)

**Primary outcome:** Inherited genetic diseases  
There were no configuration or language restrictions.

**Outcomes:** The primary outcome was the occurrence of genetic diseases in the offspring of pregnancies of couples which included a father of a certain age, considered advanced.

## Search methods

We conducted a search strategy in MEDLINE (OVID), EMBASE, and the Central Cochrane Controlled Trials Register (CENTRAL) from encompassing the full catalogue up until October 2022 (Appendix 1). Keywords were used in medical terms in their different languages: (MeSh), Entree language, and related text words.

## Collection of data

We first examined on a title/abstract level, and then, retrieved the complete articles. We

reviewed the full-text studies with a pre-specified inclusion and exclusion criteria. Then, we collected data using a standardized format, which contained the study design, participants, variables, comparisons, and results. We confirmed the data entry and verified the information for greater accuracy. We solved disagreements by consensus between two researchers.

### Synthesis of the results

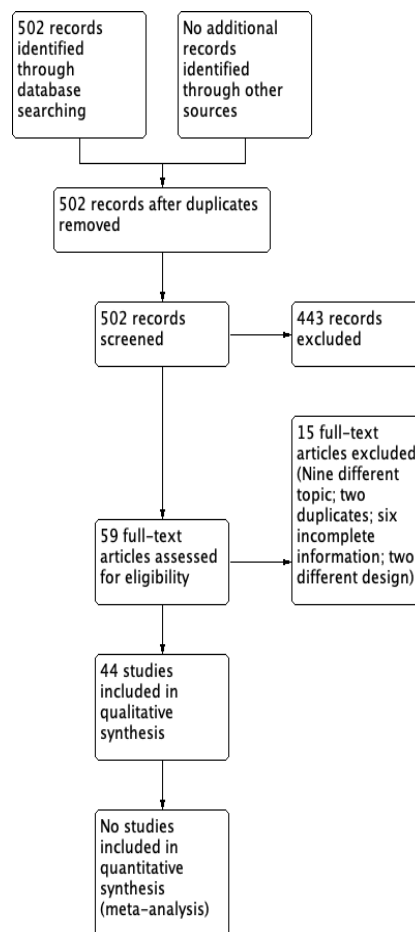
We could not perform Meta-analysis given the clinical and methodological heterogeneity presented in the studies.

## Results

### Studies selection

We identified 502 studies through the search. After excluding duplicates, we included 44 records in the qualitative analysis (Figure 1).

Figure 1. Flowchart of study selection



### Characteristics of Included studies

We included 47 records in Table 1:

**Table 1. Characteristics of included studies**

AUTHOR	YEAR	OUTCOME	PATERNAL AGE (CATEGORIZATION)
Naguib <i>et al.</i> <sup>(11)</sup>	1999	Trisomy 18	<30, 30-35, 35-40, 40-45, 45-50, 50-55, >/=55
Rintala <i>et al.</i> <sup>(12)</sup>	2017	Obsessive-compulsive disorder, tourette syndrome	<19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, >/=50
Contreras <i>et al.</i> <sup>(13)</sup>	2017	Lymphomas, leukemias, ALL, AML, Hodgkin lymphoma, NHL, Burkitt lymphoma	<25, 25-29, 30-34, 35-39, 40-44, >/=45
Contreras <i>et al.</i> <sup>(13)</sup>	2017	Leukemias, lymphoma, CNS tumor, neuroblastoma and other peripheral nervous system tumors, retinoblastoma, renal tumors, hepatic tumors, malignant bone tumors, soft tissue sarcomas, germ cell tumors, other malignant epithelial neoplasms and malignant melanomas, other and unspecified malignant neoplasms, ALL, AML, Hodgkin lymphoma, NHL, Burkitt lymphoma, ependymomas, astrocytomas, intracranial and intraspinal embryonal tumors, medulloblastomas, other specified intracranial and intraspinal neoplasms, unspecified intracranial and intraspinal neoplasms, nephroblastoma and other nonepithelial renal tumors, neuroblastoma and ganglioneuroblastoma, hepatoblastoma, Rhabdomyosarcoma, melanoma	<25, 25-29, 30-34, 35-39, 40-44, >/=45
Hurley & DeFranco, <sup>(14)</sup>	2017	Preeclampsia, preterm birth <37 ss, fetal growth restriction, major fetal anomaly, genetic disorder, infertility drugs and/or insemination, assisted reproductive technologies	<30, 30-39, 40-49, 50-59, >/=60
Sotonica <i>et al.</i> <sup>(15)</sup>	2016	Down syndrome	NA
Bilder <i>et al.</i> <sup>(16)</sup>	2013	Intellectual disability	<20, 21-34, >34
Fountoulakis <i>et al.</i> <sup>(17)</sup>	2018	Schizophrenia spectrum disorders (SSD), schizophrenia spectrum disorders (SSD)	>25, >30, >40
Eisenberg <i>et al.</i> <sup>(18)</sup>	2013	Infertility disturbances	NA
Marsidi <i>et al.</i> <sup>(19)</sup>	2021	Perinatal outcomes (aneuploidy)	≤45, >45 years
Bartoli <i>et al.</i> <sup>(20)</sup>	2017	Aneuploidy	NA
Fahmideh <i>et al.</i> <sup>(21)</sup>	2018	Non-familial and familial neurofibromatosis	<25, 25-29, 30-34, 35-39, >/=40
Fahmideh <i>et al.</i> <sup>(21)</sup>	2018	Non-familial and familial neurofibromatosis	<25, 25-29, 30-34, 35-39, >/=40
Fahmideh <i>et al.</i> <sup>(21)</sup>	2018	Combined facomatosis	20-24, 25-29, 30-34, 35-39, 40-44

*Keep going*

AUTHOR	YEAR	OUTCOME	PATERNAL AGE (CATEGORIZATION)
McGrath <i>et al.</i> <sup>(22)</sup>	2014	Any psychiatric disorder, mental and behavioral disorders due to psychoactive substance use, mental and behavioral disorders due to alcohol use, mental and behavioral disorders due to cannabis use, schizophrenia and related disorders, schizophrenia, schizoaffective disorder, mood disorders, bipolar disorder, neurotic, stress-related, and somatoform disorders, eating disorders, anorexia nervosa, specific personality disorders, mental retardation, pervasive developmental disorders, childhood autism, behavioral and emotional disorders with onset usually occurring in childhood and adolescence, hyperkinetic disorders	12-19, 20-24, 25-29, 30-3, 35-39, 40-44, >/=45
Larfors <i>et al.</i> <sup>(23)</sup>	2012	Leukemia (childhood, adult, mieloid, lymphoid)	<20, 20-34, >/=35
Barbosa-Buck <i>et al.</i> <sup>(24)</sup>	2012	Skeletal dysplasia	25-29, >39
Snajderova <i>et al.</i> <sup>(25)</sup>	2011	Sporadic neurofibromatosis 1	19,2-48,3
Yip <i>et al.</i> <sup>(26)</sup>	2006	Non-hodgkin lymphoma, leukemia	<25, 25-29, 30-34, 35-39, >40
Yip <i>et al.</i> <sup>(26)</sup>	2006	Retinoblastoma, leukemia, central nervous system cancer, astrocytoma, Wilms tumor, non-Hodgkin lymphoma	<25, 25-29, 30-34, 35-39, >40
Zhu <i>et al.</i> <sup>(27)</sup>	2005	Extremities, musculoskeletal system	<20, 20-29, 35-39, 40-44, 45-49, >/=50
Zhu <i>et al.</i> <sup>(27)</sup>	2005	Circulatory system	<20, 20-29, 35-39, 40-44, 45-49, >/=50
Zhu <i>et al.</i> <sup>(27)</sup>	2005	Nervous system, eye, ear, face and neck, circulatory system, respiratory system, cleft lip/palate, digestive system, genital organs, urinary system, extremities, musculoskeletal system, skin, hair and nails, other and unspecified, syndromes of multiple systems, Down's syndrome, other syndromes	20-29, 35-39, 40-44, 45-49, >/=50
Malini & Ramachandra. <sup>(28)</sup>	2006	Down syndrome	18-24, 25-29, 30-34, 35-40, >/=41
De Souza <i>et al.</i> <sup>(29)</sup>	2009	Down syndrome	NA
McIntosh <i>et al.</i> <sup>(30)</sup>	1995	Defects in the neural tube, anencephaly, spina bifida, microcephaly, hydrocephaly, congenital cataracts, palate, palate and cleft lip, tracheoesophageal fistula, pyloric stenosis, atresia Intestine, hirshprung disease, hypospadias, renal agenesis, kidney cystic defects, urethral atresia, short limbs, condrodistrofia, diaphragh anomaly, down syndrome	<20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, >/=50
de Michelena <i>et al.</i> <sup>(31)</sup>	1993	Down syndrome	</= 20, 21-29, 30-34, </=34, 35-39, >/=40
Byrne <i>et al.</i> <sup>(32)</sup>	2003	Schizophrenia	<20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, >/=55
Al-Gazali <i>et al.</i> <sup>(33)</sup>	2003	Achondroplasia, thanatophoric dysplasia	NA
Orioli <i>et al.</i> <sup>(34)</sup>	1995	Achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta	NA
Burd <i>et al.</i> <sup>(35)</sup>	1999	Tourette syndrome	NA

Keep going

AUTHOR	YEAR	OUTCOME	PATERNAL AGE (CATEGORIZATION)
Bunin <i>et al.</i> <sup>(36)</sup>	1997	Sporadic neurofibromatosis 1	NA
Catherino <i>et al.</i> <sup>(37)</sup>	2018	Aneuploidy	NA
Carrasquillo <i>et al.</i> <sup>(38)</sup>	2018	Aneuploidy	40-44, 45-60, and 60+
Olson <i>et al.</i> <sup>(39)</sup>	1993	Wilms tumor	<20, >55
Sharpe <i>et al.</i> <sup>(40)</sup>	1999	Wilms tumor	</=24, 25-29, 30-34, >/=35
Fisch <i>et al.</i> <sup>(41)</sup>	2003	Down syndrome	NA
Yoon <i>et al.</i> <sup>(42)</sup>	1996	Down syndrome	NA
Stener <i>et al.</i> <sup>(43)</sup>	1991	Down syndrome (Meiosis I- II)	<25, 25-29, 30-34, 35-39, >/=40
Hook <i>et al.</i> <sup>(44)</sup>	1981	Down syndrome	NA
Kaplan <i>et al.</i> <sup>(45)</sup>	1990	Retinitis pigmentosa (severe cases, sporadic)	NA
Chudal <i>et al.</i> <sup>(46)</sup>	2014	Bipolar disorder	<20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, >/=50
Fond <i>et al.</i> <sup>(47)</sup>	2017	Current and premorbid intellectual ability, working memory, visual attention & speed of processing, executive functions, verbal abilities.	NA
Sørensen <i>et al.</i> <sup>(48)</sup>	2014	Schizophrenia spectrum disorders (SSD), schizophrenia spectrum disorders (SSD)	12-24, 25-29, 30-34, 35-39, 40-44, >/=45
Urhoj <i>et al.</i> <sup>(49)</sup>	2015	Overall musculoskeletal, limb anomalies, craniosynostosis, skeletal dysplasias, syndromic musculoskeletal, and other musculoskeletal	NA
Gingold <i>et al.</i> <sup>(50)</sup>	2015	Aneuploidy	≤35; 35-38; 38-41; 41-43; and >43
Crump <i>et al.</i> <sup>(51)</sup>	2015	Brain tumors	NA

## Characteristics of the excluded studies

The studies excluded treated different topics or had a different study design.

### Outcomes

#### 1) Wilms Tumor

We found three studies about Wilms tumor.<sup>(26,39,40)</sup> Only one of them found an increased risk for fathers >55 years, compared to those <20 years, with an OR of 2.1.<sup>(39)</sup>

#### 2) Down Syndrome

Various studies focused on Down Syndrome.<sup>(15,17,27,41)</sup> Two of them found no association between the two variables.<sup>(31,42)</sup> One of them, found an increasing adjusted relative risk for Down syndrome with increasing paternal age. The older fathers (>50 years) had twice the risk for bearing offspring with the syndrome (OR=2.0; 95% CI 1.0 to 3.9) than 25-29-year-old fathers. The same study also found a strong association for Down syndrome, with the offspring of the youngest men (<20 years) having a nearly four-fold risk (OR=3.8; 95% CI 1.8 to 8.1) as the men aged 25-29 years.<sup>(30)</sup>

Others found that the rate of this disease for maternal and paternal age greater than 40 years was six-fold compared with parental ages less than 35 years.<sup>(40,41)</sup> They found a significant effect when the age factors combined (paternal and maternal) ( $p = 0.0004$ ). For paternal age  $>40$  years and maternal age  $>35$  years, there was a two-fold increase for this syndrome, compared with younger men ( $<24$  years). Nonetheless, there was no increase in Down syndrome with those below 35 years. So, they concluded that, when maternal or paternal age were considered without the interaction of the other parent's age, there was no apparent relationship. There was another study,<sup>(43)</sup> that found that fathers 41 years and older, independent of the mother's age, had a strongly increased risk for having offspring with Down syndrome. They found a significant increased risk when associated with higher mother's age ( $p=0.03$ ).

In British Columbia Registry for Handicapped Children, authors found that the mean paternal age was about half a year greater than the entire population of live births after controlling for maternal age ( $p=0.05$ ). They encountered an increase of 1.024-fold for each year of paternal age, after adjusting for maternal age.<sup>(44)</sup>

Another study found that the prevalence of Down syndrome increased with increasing paternal age at a statistically significant level ( $p=0.05$ ). They also found that, when children with Down's syndrome were excluded from the study, the association was slightly reduced.<sup>(27)</sup>

One of the studies reviewed the association of mother, father, and maternal grandmother's age, with Down Syndrome incidence. They found that the effect of age of mother and father was smaller than the effect of maternal grandmother age. Nonetheless, for every year

of father's age, there was a significant ( $p<0.001$ ) relation with Down Syndrome.<sup>(28)</sup>

The estimated odds ratio for Down syndrome associated with a 10-year increase in paternal age was 1.13, 95%CI (0.85 to 1.52). Authors concluded that there was no association between paternal age and Down syndrome. Nevertheless, the estimated effect is much smaller than the effect of maternal age.<sup>(29)</sup>

### 3) Trisomy 18

Only one of the included studies, evaluated the relationship of Trisomy 18 and paternal age.<sup>(11)</sup> There was an OR for paternal age  $>45$  of 1.90 (95% CI: 0.83 to 4.41). So, they concluded that Trisomy 18 was not related to paternal age.

### 4) Retinitis Pigmentosa

Also, only one of the studies studied the association between Retinitis Pigmentosa and father's age (46). They found that, for the clinically related late onset-mild sporadic form, the mean paternal age differs from the general population ( $p<0.001$ ). The paternal age was not higher in other types.

### 5) Hematologic malignancies

We found four studies regarding hematologic malignancies. One of them,<sup>(23)</sup> found a statistically significant association between increasing paternal age and childhood acute lymphoblastic leukemia, with an unadjusted OR of 1.04 per 5-year increase in age. They found that the risk increase remained after adjustment for maternal age and for potential confounders, but it was no longer statistically significant. In contrast, the risk of adult acute myeloid leukemia



significantly decreased among offspring to the oldest parents.

Another one did not find a significant relationship between circulatory malformations, and advanced paternal age.<sup>(27)</sup>

One of the studies,<sup>(26)</sup> found that, without considering the effect of maternal age, the paternal age was significantly associated with leukemia. The group of oldest fathers (>40 years) had an IRR 1.31, 95%CI 1.04 to 1.66. On the other side, there was no statistically significant relationship between non-Hodgkin lymphoma, and advanced paternal age.

The other study observed an increased risk of leukemia and non-Hodgkin lymphoma for the offspring of advanced age fathers.<sup>(13)</sup> Nevertheless, the risk disappeared after maternal age adjustment. For parental age as continuous variables per 5-year increase in age, they found an increased risk of leukemia, particularly acute lymphoblastic leukemia. After combined adjustment, once more, associations were diminished for older paternal age.

## 6) Mental and neurocognitive disorders

Nine studies analyzed the association between paternal advanced age, and mental and neurocognitive disorders.<sup>(22,46)</sup> One of them found that advanced paternal age was associated with a wide range of cognitive dysfunctions.<sup>(47)</sup> Even though, after multivariate analyses, the only significant difference was the age at onset.

Another one studied the association between parental age and bipolar disorder.<sup>(46)</sup> After adjusting for confounding factors, offspring of fathers aged  $\geq 50$  years had 2.8-fold increased odds of bipolar disorder, as compared to those with fathers aged 30–34 years. The odds were also increased in fathers aged 20–24 years. All

these findings were statistically significant.

One of them found that the offspring of older parents had increased risk compared with those of parents aged 25 to 29 years for a mental health disorder.<sup>(22)</sup> Nonetheless, when particular disorders were analyzed, the relationship changed. The older fathers increased the risk of schizophrenia, mental retardation, and autism spectrum disorders. In contrast, those from young fathers increased the risk of substance abuse, hyperkinetic disorders, and mental retardation.

One of the studies found schizophrenia associated with advanced paternal age.<sup>(32)</sup> There was a persistent risk for paternal age >50 years, after controlling for socioeconomic factors and family psychiatric history.

Another study found a direct correlation with educational length.<sup>(48)</sup> Conscripts born from fathers aged >40 years had a higher proportion of schizophrenia spectrum disorder and psychiatric admissions among their siblings.

One study showed that patients with schizophrenia, and also patients with other mental disorders, manifested a statistically significant higher paternal age, compared to controls.<sup>(17)</sup> They concluded that there seems to be a higher risk for the development of schizophrenia in offspring from advanced age fathers.

Another one found a significant association between intellectual disability risk and paternal age.<sup>(16)</sup> Both mild and severe cases demonstrated a significant association with advanced paternal age.

One study reported that offspring from younger fathers had no increased risk of Tourette syndrome and chronic tic disorder, in contrast with the previous studies.<sup>(12)</sup>

Also, another study reported that each additional year of paternal age decreases the risk

of Tourette disorder by 9.1%.<sup>(35)</sup> Nonetheless, this was a nonsignificant finding.

## 7) Neurofibromatosis

Three studies evaluated the association between neurofibromatosis and advanced paternal age.<sup>(21,25,36)</sup> One of them reported increased risk of non-familial neurofibromatosis for offspring of fathers aged 35–39 years, and  $\geq 40$  years (significantly higher).<sup>(21)</sup>

Another study found a significant difference between the mean paternal age at birth of Neurofibromatosis 1 sporadic cases.<sup>(25)</sup>

Another one found no association among these fathers of patients with Sporadic Neurofibromatosis 1 and control subjects ( $p=0.07$ ). There was no change when adjusted for socioeconomic status or maternal age.<sup>(36)</sup>

## 8) Other musculoskeletal diseases

Eight more studies discussed the relationship between advanced paternal age, and other musculoskeletal diseases. One of them found that for non-familial phakomatoses, other than neurofibromatosis 1, the risk estimate for offspring of fathers aged  $\geq 40$  years was higher, but non-statistically significant. Also, they found that paternal age was not associated with familial phakomatoses.<sup>(21)</sup>

Another one studied achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta.<sup>(34)</sup> It showed an increased risk of achondroplasia and thanatophoric dysplasia with advanced paternal age. The increased risk of thanatophoric dysplasia, occurred earlier (35-39-year-old group) than that of achondroplasia (40-44-year-old group). They also reported that fathers aged 35 years and older

had a 3.5-fold greater risk to have a child with a spontaneous mutation for achondroplasia. This risk was the same even if the mother was younger than age 30 years. In thanatophoric dysplasia, the risk for fathers aged 35 years and older was 3-fold that of younger ones, but only double when mothers were younger than age 30 years. In osteogenesis imperfecta, they found that there was no risk increase for fathers age 35 years and older for having a child with spontaneous mutations.

One of the studies, included an analysis of the relationship between advanced paternal age and defects of upper and lower limbs, and also chondrodysplasias.<sup>(30)</sup> They found that for chondrodystrophy, the offspring of the oldest fathers (45-49 years) showed the greatest risk. For defects of the upper limb, they noticed a trend of increasing risk, except for the 45–49-year-old group. They also found weaker associations with younger paternal age for reduction defects of the upper limb.

Another study, found that the prevalence of syndromes of multiple systems increased with increasing paternal age, and, to a lesser extent, for malformations of extremities.<sup>(27)</sup>

One study, described that fathers in the highest quintile of paternal age for the general population had a statistically significant higher relative risk to have a child with sporadic OI compared with fathers in the lowest quintile.<sup>(52)</sup>

Another one, found that there was no statistical difference between the ages of the fathers for non-inherited achondroplasia compared to the controls.<sup>(33)</sup>

Another study reported slightly higher significant risk for musculoskeletal congenital anomalies per 10-year increase in paternal age.<sup>(49)</sup> They found a 26% excess risk for fathers aged 50 or older years compared to fathers

aged 30–34 years. They examined the relation for subgroups of musculoskeletal congenital anomalies also. For limb anomalies, craniosynostosis, and skeletal dysplasia, and other musculoskeletal congenital anomalies, they found that fathers aged 50 and older years had the highest risk estimate compared to fathers aged 30–34 years. In the same group, no clear associations were seen in the rest of the paternal age groups. Regarding limb reductions, complete absence of a limb, polydactyly, syndactyly, and club foot, they found higher estimates for fathers aged 50 years and older compared to fathers aged 30–34 years, except in the club foot subgroup where they did not find any association. Nonetheless, despite positive estimates, there were no clear linear trends per 10-year increase in paternal age in any of the subgroups for limb anomalies, craniosynostosis, skeletal dysplasia, and other musculoskeletal congenital anomalies. In the subgroup of syndromic musculoskeletal congenital anomalies, an excess risk was found for children born to fathers aged 40 years and older compared to fathers aged 30–34 years. Among fathers aged 40–44, 45–49, and 50 years, and older, the excess risk was 38%, 45%, and 42%, respectively. They also studied the relationship between paternal age and other subgroups: facial appearance, short stature, extremities, early overgrowth, Marfan, and other skeletal changes. They found a similar risk in these specific subgroups to those found for syndromic musculoskeletal congenital anomalies; however, in the specific subgroups short stature, extremities, and marfan.

The Clinical Epidemiology of Skeletal Dysplasia in South America found that mean parental ages had higher values in cases than controls.<sup>(24)</sup> However, logistic regression

showed paternal age higher than 39-year as a statistically significant risk factor for osteochondrodysplasias, regardless of maternal age. They found that, except for autosomal recessive osteochondrodysplasias and for lethal osteogenesis imperfecta, for which paternal age was not different from controls, a significant association with paternal age was found for achondroplasia, thanatophoric dysplasia, non-lethal osteogenesis imperfecta, and all the other autosomal dominant osteochondrodysplasias.

### 9) Embryo aneuploidies

Five studies analyzed the relationship between embryo aneuploidies and paternal age. One of them found that embryo aneuploidy was significantly greater for all men aged >40 years when compared to men <34 years ( $p < 0.001$ ) when using donor eggs.<sup>(18)</sup> They reported that no significant difference in embryo aneuploidy was seen between groups of men aged 40–44, 45–60, and 60 and older.

Another one evaluated the effect of paternal age in embryos.<sup>(37)</sup> Authors found that controlling for donor oocyte age, there was no significant association between male partner age and in vitro fertilization laboratory outcome; neither it significantly impacted the aneuploidy rate ( $p 0.20$ ); even when aneuploidy was categorized by the affected chromosomes' size and centromere position. They also described that paternal age did not impact the odds of sex chromosome aneuploidy (OR 0.98 95%CI 0.89 to 1.08) or incidence of trisomy 21 ( $p 0.73$ ) or trisomy 22 ( $p 0.054$ ).

Another study found that the aneuploidy rate for advanced paternal age blastocysts and the good quality blastocyst conversion rate

from fertilized zygote were equivalent to in vitro fertilization cycles using young females with non-advanced paternal age. Nevertheless, chromosome error analysis revealed a trend towards an increase in sex chromosome aneuploidies of advanced paternal age blastocysts 7.2% vs. 4.9% ( $p$  0.15).<sup>(49)</sup>

The last one found that male partner age was not significantly associated with aneuploidy rate at any age.<sup>(50)</sup>

## 10) Perinatal complications

Only one study reviewed the relationship between perinatal complications and paternal age.<sup>(14)</sup> They reported that the frequency of perinatal complications was higher in the youngest (<30 years) and oldest ( $\geq 60$  years) paternal age groups. They reported that adjustment for maternal age resulted in null independent influence of paternal age on adverse pregnancy outcomes. That is so, they concluded that the observed influence of paternal age was attributable primarily to concordant similar extremes of maternal age. Of note, the use of assisted reproductive technology in live births significantly increased as paternal age increased with 0.1% of pregnancies achieved with assisted reproductive technology when paternal age was <30 compared to 2.5% when >60 years of age ( $p$  <0.001). They also noted that after accounting for the confounding influences of maternal age, race, Medicaid status and multifetal gestation, increased paternal age was not associated with a significant increase in the rate of pre-eclampsia, preterm birth, fetal growth restriction, congenital anomaly, genetic disorder or neonatal intensive care admission with analyses stratified by use of assisted reproductive technology.

## 11) Cancer

Three studies described different cancer incidences and their relationship with advanced father's age. The biggest one which we previously mentioned reported that there was an increased risk of cancer overall and leukemias, for older maternal and paternal age without mutual adjustment.<sup>(13)</sup> With mutual adjustment associations were attenuated for older paternal age. For paternal age, the risk of Wilms tumor appeared elevated with older age (OR 1.11, 95% CI: 0.97-1.28). They found no notable associations by laterality for retinoblastoma and Wilms tumor, although an elevated risk was observed for bilateral Wilms with paternal age over 35 in crude analyses. Additionally, they found that the effect of paternal age among younger mothers was null for fathers 30–34 years and the 35+years compared to fathers <30 years (Adjusted OR 0.95, 95% CI: 0.80-1.12, Adjusted OR 1.00, 95% CI: (0.77 to 1.30), respectively).

Another one which studied brain tumors, found that parental age was not associated with brain tumors overall.<sup>(51)</sup> The third one already mentioned that paternal age was not associated with the risk of developing retinoblastoma, irrespective of maternal age.<sup>(26)</sup> Also, they found no significant paternal age effects in childhood central nervous system cancer, before adjustment of the mother age effect. Noteworthy, with adjustment of maternal age, they found a positive trend ( $p$  <0.01) for increasing risk in central nervous system cancer. Of importance, the risk in central nervous system cancer for all age groups >30 years increased, with highest risk (IRR 5 1.69; 95% CI 1.21 - 2.35) in the age group >40 years. The results of astrocytoma were like those of all central nervous system cancer. No significant association was found

between paternal age and Non-Hodgkin lymphoma, or Wilms tumor.

## 12) Other congenital malformations

There were two studies about various congenital malformations and its relationship with paternal age. One of them found that for neural tube defects in general, meaning: anencephaly and/or spina bifida, there was an overall trend of increasing risk with increasing paternal age.<sup>(30)</sup>

They reported that risk increased for each age group category above referent group (25-29 years), except for men in the 45-49 years category. A similar pattern was reported for both anencephaly and spina bifida, individually. They found that cataracts also showed a trend of increasing risk, except for the 45-49-year-old group. The analysis of microcephaly, hydrocephalus, tracheoesophageal fistula, atresia of the large intestine, anomalies of the diaphragm, cleft palate, cleft lip with or without cleft palate, hypospadias, atresia of the urethra, found some elevated odds ratios for age categories over 29 years, but the estimates did not follow a monotonic pattern. In addition, they reported that many estimates were imprecise, as reflected in the wide confidence intervals. They found no consistent association with older paternal age and pyloric stenosis, obstructive renal defects, cystic kidney, Hirschsprung's disease, or renal agenesis. Interestingly, they also found that several defects showed an association with younger paternal age (<20 years). As we already said before, they found a strong association for Down syndrome, with the offspring of the youngest men. For neural tube defects combined, offspring of fathers less than 20 years of age had the highest elevation in risk (OR 2.6; 95% CI 1.2-5.6). They found a similar pattern

for anencephaly, spina bifida, hydrocephalus, hypospadias, cystic kidney, and anomalies of the diaphragm. A weaker association was described for younger paternal age and cleft palate, cleft lip with or without cleft palate, tracheoesophageal fistula, atresia of the large intestine, reduction defects of the upper limb, reduction defects of the lower limb, atresia of the urethra, and obstructive renal defects. They saw no elevation in risk for younger paternal age for microcephaly, congenital cataracts, pyloric stenosis, chondrodystrophy, renal agenesis, or Hirschsprung's disease.

The other one reported that there were no differences in the prevalence of congenital malformations in different paternal age groups.<sup>(27)</sup> However, they observed that prevalence of syndromes of multiple systems increased with increasing paternal age, and, to a lesser extent, for malformations of extremities. When children with Down's syndrome were excluded, the association between paternal age and syndromes of multiple systems was slightly reduced.

## Discussion

Nowadays, given the tremendous changes in health, social, and most of all, cultural scenarios, delaying childbearing has become a widespread phenomenon, mainly among developed countries.<sup>(1-3)</sup> Postponing pregnancy comes with several consequences, especially for the offspring.

The negative impact of advanced maternal age on reproductive outcomes has been widely studied and is well documented. It has been linked to decrease in fertility rates, increase in miscarriage rates, pregnancy complications, congenital anomalies, and perinatal mortality.<sup>(1,4,5)</sup>

Just as maternal age is of concern, paternal age, independently from the former, should also be a topic of interest. Even if it is still not as clear, advanced paternal age has been correlated to negative outcomes both for the pregnancy, and for the newborn.<sup>(6-9)</sup> One of the most important things is that there is no obvious cut-off point beyond which paternal age should be considered as 'advanced'; that is, a dose-dependent model is proposed instead.<sup>(53,54)</sup>

The main biological hypothesis proposed to explain the effects of advanced paternal age is called the "copy error".<sup>(55,56)</sup> This hypothesis states that the numerous cell divisions during spermatogenesis allow for the introduction of transcription errors during replication, which are then propagated as gene mutations. This idea relies on the basis that by the age of 35 years, the spermatozoa have undergone roughly 540 divisions and replications, and there is data showing that several conditions due to new, dominant mutations, are associated with older paternal age.<sup>(57)</sup> However, some new data has indicated that a simple copy error model may not be a primary mechanism underlying some conditions.<sup>(56)</sup> It is also reasonable to suggest that advanced paternal age may be associated with an adverse psychosocial environment for the offspring, such as unwanted pregnancy, and that older fathers may have certain personality traits that would result in an increased age of parenthood.<sup>(58)</sup>

The reason that an important paternal age effect is found for some conditions resulting from new germinal mutations but not for others is not totally understood. Some authors have hypothesized that all autosomal dominant conditions in their sporadic form should have a paternal age effect of similar magnitude, and that the observed differences

among conditions result from the inclusion of misdiagnosed, familial or somatic mosaic cases, or from methodologic limitations of specific studies.<sup>(36,59)</sup> Another proposed hypothesis is based on the variation in the susceptibility of specific genes to copy errors, the existence of a maternal effect. It proposes that the paternal age effect is not of the same magnitude for all autosomal dominant mutations and may even not exist at all for some conditions.<sup>(36)</sup>

Some studies have reported conflicting results for paternal age and birth defects, but they often evaluated only a single defect or a small group of defects, or they included a limited study size.

We found no statistically significant association between advanced paternal age and anomalies such as Trisomy 18, Obsessive Compulsive Disorder, Tourette syndrome, schizoaffective disorder, and eating disorders, adverse perinatal outcomes (pre-eclampsia, pre-term birth, fetal growth restriction, or neonatal intensive care admission), acute lymphoblastic leukemia, childhood acute myeloid leukemia, adult leukemia, autosomal recessive osteochondrodysplasias, lethal osteogenesis imperfecta, microcephaly, hydrocephalus, tracheoesophageal fistula, atresia of the large intestine, pyloric stenosis, reduction of the lower limb, anomalies of the diaphragm, cleft palate, cleft lip with or without cleft palate, hypospadias, atresia of the urethra, chondrodystrophy, obstructive renal defects, cystic kidney, Hirschsprung's disease, or renal agenesis. cataracts and retinoblastoma.

On the other hand, we did find a significant relationship between older fathers and psychiatric disorders ( $\geq 45$  years), schizophrenia incidence ( $>25$  years, specially  $\geq 55$  years), and age of onset ( $>22$  years), schizophrenia spectrum disorder ( $>40$ ,  $\geq 45$  years), autism ( $\geq 45$

years), bipolar disorder syndrome ( $\geq 50$  years), intellectual disability, nonfamilial phacomatoses predisposing to nervous system tumors -most pronounced for nonfamilial neurofibromatosis (NF) type 1 ( $\geq 30$ ,  $\geq 32$  years,  $> 35$  years,  $\geq 40$  years), nervous system cancer ( $\geq 30$  years, specially  $\geq 40$  years), astrocytoma, retinitis pigmentosa, overall musculoskeletal congenital anomalies ( $> 40$  years, specially  $> 50$  years), osteochondrodysplasias ( $> 39$ -year old), non lethal osteogenesis imperfecta, all the other autosomal dominant osteochondrodysplasias, syndromes of multiple systems, combined neural tube defects (anencephaly and/or spina bifida), reduction defects of the upper limb,  $\geq 25$ , except for fathers 45-49 years old).

Regarding neurofibromatosis, there is evidence that the majority of de novo NF1 and NF2 mutations are of paternal origin.<sup>(60,61)</sup> Also, a paternal age effect for this disease, specially sporadic NF1, has been reported consistently, although the age difference has not always been statistically significant.<sup>(36,62)</sup>

The literature shows the increase of both mean paternal age and age difference of the parents in dominant retinitis pigmentosa (38.8 + 4.7 years) as compared with the mean age of fathers in the general population (29.1 years,  $p < 0.001$ ).<sup>(63)</sup>

Since the 80's, advanced parental age has been proposed to constitute a generic risk factor for the development of any mental disorder.<sup>(64)</sup> Nonetheless, the evidence also found an increased risk for younger fathers. However, there are only a few studies that examined the effect of paternal age across different diagnostic categories simultaneously.<sup>(64-66)</sup>

Of note, we found that the association between paternal age and mental disorders, followed a U shape, meaning that there was a

higher incidence for older, but also, younger fathers offspring. For instance, for schizophrenia, we found an increased incidence for fathers  $\geq 40$  years, and  $\leq 20$  years. The literature strongly supports our findings.<sup>(32,67-71)</sup> For instance, one meta-analysis concluded that higher paternal age doubles or triples the risk for schizophrenia in the offspring of men above 40 years of age but also of fathers younger than 25 years old.<sup>(72)</sup> Another meta-analysis suggested that parental age  $> 55$  years constitutes a risk,<sup>(73)</sup> while a third one reported that both parental ages  $< 20$  and  $> 35$  constitute a risk factor.<sup>(74)</sup>

Neural tube defects are also well studied. For some of them there is strong evidence supporting a direct association between paternal age and incidence of illness, while there is conflicting information about others. Data conflict on whether there is a relation between paternal age and defects such as hydrocephalus and oral clefts.<sup>(30)</sup>

We found something similar for schizophrenia, for neural tube defects combined. The risk was higher for  $< 20$  years-old fathers too. The same pattern was seen for anencephaly, spina bifida, hydrocephalus, hypospadias, cystic kidney, and anomalies of the diaphragm. Weaker associations were found with younger paternal age for cleft palate, cleft lip with or without cleft palate, tracheoesophageal fistula, atresia of the large intestine, reduction defects of the upper limb, reduction defects of the lower limb, atresia of the urethra, and obstructive renal defects.

There were opposite findings regarding embryo aneuploidies. Some studies reported a significant relationship between older fathers ( $> 40$  years) and embryo aneuploidy, others reported that despite a trend towards decreased fertilization, blastulation, and biopsy rates,



advancing paternal age does not have a statistically significant impact on in vitro fertilization outcomes or aneuploidy rates, and others found that fertilization rates were significantly reduced with advanced paternal age sperm, even though embryo development and overall blastocyst chromosome constitution.

We found something similar regarding hematologic malignancies. Some found a significant relationship between advanced paternal age and leukemia (>35 years) while others found that even when this effect was found, it receded after adjusting for maternal age. Same happened for non-Hodgkin lymphoma.

Also, we found opposite findings regarding thanatophoric dysplasia, and achondroplasia. Some found a significant higher incidence for fathers  $\geq 35$  years old, others found no significant relation.

Same happened for Wilms tumor. Some studies reported no relationship between father's age and the incidence of this neoplasia, while others found a higher incidence for  $\geq 55$ -year-old father's offspring.

Some previous studies demonstrate a positive relationship between parental age and incidence of sporadic Wilms' tumor, suggesting that at least some of them could result from new germline mutations in a parent. For instance, Huff et al. in 1990, demonstrated the paternal origin of seven out of eight Wilms' tumor cases with de novo constitutional deletions of chromosomal band 11p13 loci.<sup>(75)</sup> Some authors have suggested the "two-hit" hypothesis for this disease. There is no evidence, however, that parents of children with bilateral tumors tend to be older than those of children with unilateral tumor, suggesting that bilateral tumors are no more likely to be the result of new

germline mutation in a parent than unilateral tumor. This failure to confirm the predictions of the two-hit model contrasts to the finding of Pellié *et al.*<sup>(76)</sup> in 1973 that fathers of patients with sporadic bilateral retinoblastoma are more than 1.2 years older, than fathers of the general population, while fathers of sporadic unilateral retinoblastoma patients do not differ in average age from fathers in the general population.<sup>(39)</sup>

Down syndrome is one of the most studied conditions and the evidence is conflicting. Some studies report a positive association,<sup>(30,77)</sup> while some others find no significant effect.<sup>(8)</sup> The same was found in this study. We also found no consensus for Down syndrome. Some studies reported no significant relationship while others reported a significant increased risk for fathers  $\geq 41$  years old, or >50 years old. Of note, the same U shape as for mental disorders, was found for this disease. The incidence was higher for <20 and 25-29 year-old-father offspring too.

### Strengths and limitations

This is the first systematic review that seeks an association between paternal age and genetic diseases. This type of review can provide valuable information for future decision making for couples considering childbearing.

Regarding the limitations, there was not enough homogeneity among the studies we included, not even in defining the age considered *advanced*, and neither in the evaluated outcome. Nevertheless, the fact that associations have been found, between paternal age and so many different outcomes, makes it important to carry future investigation efforts around this topic.



## Conclusions

We found a tendency of association between older fathers and psychiatric disorders (schizophrenia, autism, bipolar disorder syndrome, intellectual disability), nervous system cancer and musculoskeletal congenital anomalies.

In contrast, we did not find associations between advanced paternal age and anomalies such as Trisomy 18, Obsessive Compulsive Disorder, Tourette syndrome, schizoaffective disorder, adverse perinatal outcomes, hematologic disturbances, microcephaly, hydrocephalus, gastrointestinal disturbances, cleft lip with or without cleft palate and genitourinary disturbances.

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