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# Short duration of marriage at conception as an independent risk factor for schizophrenia

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ABSTRACT

Short duration of marriage (DoM) is a risk factor for preeclampsia that is also related to the risk for schizophrenia. This analysis examined the risk for schizophrenia associated with DoM and its independence from parental psychiatric disorders, parental ages and fathers' age at marriage.

*Method:* Relative Risks (RR) for schizophrenia were estimated using continuous and stratified Cox proportional hazards models in the 90,079 offspring from the prospective population-based Jerusalem birth cohort study (1964–1976). Schizophrenia diagnos in offspring and parental diagnoses of schizophrenia or other psychiatric conditions were identified by cross-linkage to Israel's psychiatric case registry. DoM and paternal age at marriage were abstracted from birth certificates.

*Results:* In the full model, RR for schizophrenia decreased for each 5 years DoM: 0.83 (0.75–0.95), $p_{trend} = 0.0015$. Stratified analyses showed the greatest RR risk for DoM <2 years: 1.53 (1.11–1.66) with lesser risk for 2–4 years DoM: 1.38 (1.05–1.81) compared to more DOM of 10+ years. DoM effects were independent from parental psychiatric diagnoses (RRs = 2–6, $p$~0.00001), paternal age (1.34: $p = 0.0001$ /5 years- including fathers of 25–34 years). The apparent risk related to later fathers' age at marriage (1.27: $p < 0.0001$) was eliminated in after accounting for DoM and later paternal age.

*Conclusions:* Offspring born to couples married for less than 3 years, across all paternal ages, harbored a small increased risk for schizophrenia, which was independent of parental psychiatric disorders and paternal age. Fathers who married late had particularly short DoM, which, along with paternal age, completely explained the risks related to later paternal age at marriage. Further studies are needed to replicate these results and examine if pathogenic pathways include prenatal immune activation.



## 1. Introduction

New evidence supports a role for the intrauterine environment in mediating some genetic risk for schizophrenia. Among schizophrenia cases from several international locations, those exposed to prenatal adversity harbored an increased polygenic risk score for schizophrenia derived from a genome wide association study (GWAS). This higher genetic risk was attributable to a group of genes whose placental expression differed in complicated pregnancies, including ones for inflammation, oxidation and cellular stress responses (Ursini et al., 2018).

Preeclampsia is the most common pregnancy complication involving placental inflammation, occurring in ~3.4% of pregnancies overall, with twice the risk in first pregnancies (Ananth et al., 2013). The pathology involves potentially separate immune reactions which impair the invasion of the embryonic trophoblast into the uterine wall and the transformation of the uterine spiral arteries into the highly dilated placental vasculature, leading to restricted fetal blood flow (Weiss et al., 2016). Preeclampsia is associated with multi-system endothelial

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dysfunction and long-term cardiovascular disease in mothers and developmental abnormalities in offspring predisposing to metabolic and brain disorders (Figueiró-Filho et al., 2017), including a 2 to 4 fold increase in the risk for schizophrenia (Byrne et al., 2007; Suvisaari et al., 2012).

Maternal intolerance to the fetal (paternal) antigens is a risk factor for preeclampsia that predominates in nulliparous women and those who have changed partners (Dekker et al., 1998). A lengthy period of pre-pregnancy vaginal exposure to the sperm of the offspring's father can overcome this maternal intolerance, although other maternal inflammatory conditions are also risk factors for preeclampsia.

If maternal immune intolerance is a component pathway of the risk for schizophrenia then the couples' duration of pre-pregnancy sexual contact could be related to the offspring risk for schizophrenia. One study did demonstrate an association between short durations of marriage (DoM) and increased offspring risk for schizophrenia and considered preeclampsia as the explanation (Malaspina et al., 2001). While this effect was independent of paternal age effects, the study did not account for parental psychiatric illness or the father's age at marriage, both of which may be relevant to an inherited vulnerability for the disease that could plausibly be associated with the DoM at parturition.

It is also proposed that men who reproduce at older ages harbor more genetic vulnerability for schizophrenia that had delayed their coupling behavior, which may be inherited by his offspring as schizophrenia (Gratten et al., 2016) and, alternatively, that older men are more likely to reproduce with mentally ill women, and it is the mother's genetic risk that is transmitted (Miller et al., 2011).

DoM is an insufficient proxy for the total length of sexual cohabitation by a couple currently, in almost all developed countries. However >97% of the offspring in the 1964–1976 Jerusalem Perinatal Cohort Schizophrenia Study (JPSS) were born to married couples. Then, as now, Israel had among the lowest out of wedlock births of any country (the Organisation for Economic Co-operation and Development (OECD), 2018, November 29). The duration of the marriage at the time of each proband's birth is thus reasonably considered to be the lower limit on the length of time that the mother was vaginally exposed to the sperm of the proband's father in this cohort.

This analysis examined offspring risk for schizophrenia and separated the inter-related measures of paternal age, father's age at marriage, parental psychiatric diagnoses, and duration of marriage (DoM) by using stratified and continuous models.

## 2. Method

The analyses were conducted with data from the JPSS, which recorded all births in a defined area of Jerusalem from 1964 to 1976 (Harlap et al., 2007). Parental marriage dates were abstracted from each offspring's birth certificate and the duration of the parent's marriage at the offspring's birth was calculated as the DoM. Psychiatric diagnostic information on probands and parents were obtained by cross-linkage of the JPSS data to the Israeli national psychiatric case registry by personnel from the Ministry of the Interior. The anonymous file prepared for this analysis included the dates and diagnoses for all inpatient and outpatient admissions. For probands with any discharge diagnosis of International classification of Diseases (ICD) F10 through F20), incidence was defined as the date of first psychiatric treatment, regardless of the diagnosis at that time. For the parents, whose psychiatric diagnoses were often made using earlier ICD criteria, a broader definition of schizophrenia was used (ICD-10 F20-F29) that included schizotypal disorder, delusional disorders, non-affective psychoses, and schizoaffective disorders. As well, a category of "other" was designated to identify the parents with other psychiatric conditions, including affective disorders, anxiety, substance abuse, personality, and eating disorders (ICD-10 F30-F99) to account for possible misdiagnoses.

### 2.1. Statistical analysis

Cox Proportional hazards models, both continuous and stratified, estimated the relationships between paternal age, father's age at marriage and the DOM with the incidence of schizophrenia in offspring. These predictor variables were handled either as categories by age or years (coded 1 if present, versus 0) or as continuous or ordinal variables. As a continuous variable, father's age was transformed as deviations from the mean age (31 years) divided by five to account for its high correlation with maternal age and other variables. Father's age at marriage was handled in age groups with covariates for offspring sex (1 for male, 0 for female) and psychiatric conditions in parents, as four dichotomies coded 1 or 0 for schizophrenia or other psychiatric conditions, respectively, in fathers or in mothers. No other covariates altered the relative risk (RR) by more 10% or were independent predictors of offspring schizophrenia risk at $p \leq 0.05$. These criteria excluded specific years of birth; time as secular trend over years; season of birth (both month of birth and sin/cosine of month of birth); social class (six categories derived from paternal occupation at the time of the birth); birth order (categories for 2nd, 3rd and 4th+, versus 1st births); parents' years of education (0–8, 9–12 and unknown, versus 13+); residence of parents at the time of the offspring's birth (rural versus urban); religion of parents (Jews versus others); parents' places of birth (Israel versus abroad); and parents' ethnic ancestry based on each grandfather's place of birth (Israel, other Western Asia, North Africa, Europe or developed countries).

Observations were timed for each offspring from birth until date of death or admission to psychiatric treatment, with censoring on December 31, 2004. Efron's method was used to handle ties. Assumptions of proportionality were verified by inspections of "log-negative-log" plots and testing each variable as a time-dependent product of its coded value (0, 1) with length of follow-up. To account for correlations between siblings, the analyses were aggregated within families based on the mothers.

## 3. Results

### 3.1. Subject characteristics

The vast majority of probands were born to married mothers (97.4%), 0.09% to divorced, 0.03% to widows, 0.70% to never married women. Only 40 mothers were previously married and 10 were widowed. Four-fifths of the remaining 1.75% had stable partnerships, based on interviews. Sixty-three % of offspring were first births. Paternal birth years ranged from 1880 to 1960; fathers were age 16–80 years at the births (mean = 30.5 ± 6.8 SD, median = 30). Maternal age categories (years) and offspring numbers were: <25 years: $n = 30{,}062$; 25–29 years: $n = 28{,}768$; 30–34 years: $n = 17{,}914$; and 35+: years: $n = 12{,}085$. The population was equally divided among high, middle and lowest social class (Corcoran et al., 2009). Birthplaces of paternal grandfathers included Israel: 14,995; other west Asia: 27,241; North Africa: 18,639; Europe, North America; 27,954.

The probands excluded from the analysis were those who were missing the fathers year of birth ($n = 339$, 0.4%), mothers year of birth (8, 0.01%), parents' year of marriage: (1586, 1.8%) and those whose mother's age was coded as 10+ years older than father's (87, 0.1%), for a total of 1704 probands (1.9%). The excluded offspring included 16 (0.9%) with the narrow definition of schizophrenia and 21 (1.2%) with the broad definition, which was similar to the included 89.823 births (0.6% and 1.0%).

#### 3.1.1. Outcomes

There were 552 probands diagnosed with schizophrenia: 348 males and 204 females. Years representing paternal age, father's age at marriage and the duration of the marriage were significantly inter-related ($p < 0.001$) (Table 1).

**Table 1**
Paternal characteristics in terms of age categories at offspring births, numbers of offspring born to fathers in each age category, durations of marriage at his offspring's births, his ages at marriage by paternal age categories.

| Paternal characteristics | | | | | |
|---|---|---|---|---|---|
| Paternal age groups (years) | 15–24 | 25–34 | 35–44 | 45+ | Total |
| Number of offspring born to fathers in each age category: | 11,805 | 50,647 | 22,037 | 3886 | 88,375 |
| Proportion of offspring born to fathers in each age category, separate by his duration of marriage at the births: | | | | | |
| <3 years | 67.7% | 23.8% | 5.9% | 5.8% | 24.4% |
| 3–4 years | 26.1% | 24.3% | 6.6% | 5.2% | 19.3% |
| 5–9 years | 6.1% | 40.3% | 21.5% | 12.1% | 29.8% |
| 10+ years | 0.2% | 11.6% | 66.1% | 76.9% | 26.6% |
| Proportion of fathers in each age category, separated by his age at marriage | | | | | |
| <20 years | 14.2% | 3.8% | 4.4% | 1.4% | 5.2% |
| 20–24 years | 85.7% | 49.9% | 29.4% | 10.3% | 47.8% |
| 25–29 years | 0.0 | 40.7% | 35.0% | 25.3% | 33.2% |
| 30+ years | 0.0 | 5.7% | 31.2% | 63.0% | 13.8% |

Chi square $p < 0.0001$.

### 3.1.2. Duration of marriage

There were protective effects of longer DoM against risk, with each five years predicting a 14% reduction in risk, RR = 0.86 (0.79–0.95), $p_{trend} = 0.0015$.

### 3.1.3. Parental psychiatric diagnoses

Paternal and maternal diagnoses of schizophrenia and "other psychiatric diagnoses" were respectively diagnosed in 466 (1.2%) and 798 (2%) of the 39,137 fathers and in 513 (1.2%) and 672 (1.6%) of the 41,812 mothers. Table 2 shows the relationships between parental psychiatric diagnoses of schizophrenia and other psychiatric disorders.

Fathers with a schizophrenia diagnosis did not reproduce at older ages, but fathers with other disorders and mothers with any psychiatric diagnosis did bear offspring at later ages than the parents without a psychiatric diagnosis. Offspring of fathers with schizophrenia diagnosis had a four-fold increase in the risk for schizophrenia (RR = 4.30, 2.91–6.35, $p < 0.0001$), and offspring of fathers with other psychiatric conditions had a doubled risk for schizophrenia (1.99, 1.30–3.04, $p = 0.0015$), compared to offspring of fathers without a mental illness. Even larger risks were conveyed for schizophrenia by maternal diagnoses of schizophrenia (6.16, 4.39–8.62, $p < 0.0001$) and other psychiatric conditions (2.61, 1.68–4.05, $p < 0.0001$). The risks were higher for maternal transmission than paternal transmission for schizophrenia (43%) and for other psychiatric diagnoses (31%), although the differences did not reach statistical significance. Parental diagnoses were included as covariates and accounting for these did not alter the RR for DoM.

Fathers age at marriage in unadjusted analyses the categories of father's ages at marriage were significantly related to offspring schizophrenia risk ($p_{trend} < 0.04$). Compared to offspring whose fathers married before age 20 years, RRs increased at successively later fathers ages of marriage: for marriage at age: 20–24 years, RR = 0.98 (0.65–1.48), for age 25–29 years, RR = 1.17 (0.96–1.42); and for marriage at age 30 or afterwards, RR = 1.73 (1.38–2.16). After including paternal age in the model, however, only the offspring of fathers who married after age 30 years had an increased risk schizophrenia, 1.37 (1.04–1.82). The entire risk from later paternal age at marriage was eliminated by further adjustment for the duration of the marriage (RR = 1.18 (0.82–1.70)).

To further confirm that marriage duration was the meaningful variable in explaining the association between later father's age at marriage and offspring schizophrenia risk, two follow up analysis were conducted. The first only included couples that were married at least five years at the offspring's birth. In this longer-married sample, effects of successively later paternal age at marriage were attenuated compared to those of offspring whose fathers married before age 20 years (RR = 1.05 (0.91–1.21); 25–29 years, RR = 1.19 (0.91–1.57); 30–34 years, 1.32 (1.06–1.65); and 35 + years, 1.15 (1.05–1.26). Further adjustment for paternal age attenuated these risks to null. Another follow-up analysis only included fathers who married at age 30 years or later. Using slightly different duration of marriage categories to adjust for sample size, the effect of short marriage durations on RR was confirmed: <3 years, 1.71 (1.22–2.40); 3–4 years: 1.30 (0.85–1.98); 5–9 years, 1.19 (0.80–1.75) and for ≥10 years: 1.01 (0.62–1.65) in comparison to RR of all offspring with fathers who married before age 30. The effect of short DoM was the important variable conveying increased risk of schizophrenia to offspring of later married fathers.

Conversely, models that included parental psychiatric diagnoses did not diminish the risk from later father's age at marriage. In continuous models, the RR of advancing fathers age at marriage was 1.27 (1.14–1.41), $p_{trend} < 0.0001$) per decade. This risk was reduced by adjusting for paternal age (RR = 1.14 (1.01–1.30), $p_{trend} = 0.037$) and then eliminated by further adjustment for DoM (1.07 (0.93–1.24), $p_{trend} = 0.36$). Fathers who married at older ages had significantly

**Table 2**
Relationships between parental psychiatric diagnoses and paternal measures.

| | # of offspring | Fathers of probands | | | | Mothers of probands | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | % with schizoprenia | p | % with other psychiatric conditions | p | % with schizophrenia | p | % with other psychiatric conditions | p |
| Total | 88,375 | 1.2 | | 1.9 | | 1.2 | | 1.5 | |
| Duration of marriage (years) | | | | | | | | | |
| <3 | 21,555 | 1.3 | | 1.9 | | 1.2 | | 1.5 | |
| 3–4 | 17,042 | 1.3 | <0.02 | 1.8 | <0.001 | 1.1 | <0.05 | 1.4 | 0.01 |
| 5–9 | 26,312 | 1.1 | | 1.8 | | 1.1 | | 1.3 | |
| 10+ | 23,467 | 1.0 | | 2.3 | | 1.3 | | 1.7 | |
| Paternal age at birth of offspring (years) | | | | | | | | | |
| <25 | 11,805 | 1.1 | | 2.0 | | 0.9 | | 1.5 | |
| 25–34 | 50,647 | 1.2 | n.s. | 1.7 | <0.0001 | 1.1 | <0.0001 | 1.3 | <0.0001 |
| 35–44 | 22,037 | 1.2 | | 2.3 | | 1.3 | | 1.8 | |
| 45+ | 3886 | 1.2 | | 2.3 | | 2.2 | | 1.9 | |
| Fathers age at marriage (years) | | | | | | | | | |
| <20 | 4597 | 1.6 | | 2.4 | | 1.1 | | 1.3 | |
| 20–24 | 42,265 | 1.0 | <0.0001 | 1.8 | <0.0001 | 1.1 | <0.0001 | 1.4 | 0.001 |
| 25–29 | 29,292 | 1.1 | | 1.7 | | 1.1 | | 1.4 | |
| 30+ | 12,215 | 1.5 | | 2.6 | | 1.7 | | 1.9 | |

Numbers and % of offspring whose fathers or mothers were diagnosed with schizophrenia or other psychiatric conditions by paternal age, fathers' age at marriage and duration of marriage (chi square).

shorter marriage durations before reproduction, which, together with paternal age, completely accounted for the apparent influence of father's age at marriage on the risk for schizophrenia.

*3.1.4. Paternal age*

Paternal age was a significant risk factor for offspring schizophrenia in all age strata of fathers, beginning at age 30–35 years compared to offspring of fathers <25 years: The RRs = 1.14 (0.85–1.54) at 25–29 years; 1.47 (1.07–2.03) at 30–34 years; 1.79 (1.23–2.59) at 35–39 years, 1.95 (1.25–3.05) at 40–44 years, and 2.70 (1.64–4.45) for fathers 45 years or older. Each decade of paternal age multiplied the RR for schizophrenia by 1.55 (1.36–1.78), $p_{trend} = 0.0001$. Table 3 shows that the paternal age effect was not influenced by considering the parents psychiatric diagnoses, with a 38% increase per 5 years. With further adjustments for fathers age at marriage and the duration of marriage the paternal age effect remained unaltered, RR = 1.35 (1.12–1.64), $p = 0.0016$ for each five years.

*3.1.5. Duration of marriage*

The final full model included duration of marriage, parental diagnoses and paternal age. Paternal age at marriage was excluded, as it was not an independent risk factor. In this model, offspring born to shorter-married couples had the highest RR: <2 years: 1.53: (1.11–1.66), 2–4 years: 1.38 (1.05–1.81); and for 5–7 years: 1.11 (0.87–1.42) compared to offspring of parents married for 10 or more years. Alternatively, the decrease in risk for each five years of marriage was RR = 0.89 (0.82–0.97), $p_{trend} = 0.01$. The same protective effect of longer DoM was demonstrated when the model was stratified by paternal age, RR = 0.85 (0.84–0.97, $p = 0.013$).

## 4. Discussion

Offspring of parents with shorter durations of marriage demonstrated a significantly increased risk for schizophrenia, independent of the any risk associated with parents' psychiatric illness and paternal age. Those born to parents married less than two years, equivalent to about one year of pre-pregnancy sexual contact, had a 50% increase in risk for schizophrenia, and those of marriages lasting 2–4 years at parturition had a 30% increase in risk.

Without biological confirmation and replication, the explanations of this effect are speculative. This increasing risk of schizophrenia for shorter marriage durations coincides with findings from the obstetric literature showing that a shorter duration of parental sexual contact before conception increases the pregnancy risk for preeclampsia. With longer periods of vaginal exposure to a specific father's sperm, the maternal immune intolerance to paternal antigens in the embryonic trophoblast is diminished, facilitating a healthy pregnancy. Otherwise, implantation and adequate conversion of the uterine spiral arteries into a vascular placenta to support the fetus are impaired. This pathology leads to preeclampsia, the most common condition affecting the placenta. The spectrum of this complex and heterogeneous condition ranges in severity from “white coat” hypertension to preeclampsia and eclampsia (Ananth et al., 2013). Notably, the protective effects of sexual contact are partner-specific. Nulliparous women with a prior abortion have a reduced risk for preeclampsia only if the prior pregnancy was with the same partner (Saftlas et al., 2003). The incidence of preeclampsia with a new partner in a subsequent pregnancy is nearly as high as for a first pregnancy (Dekker et al., 1998; Li and Wi, 2000; Trupin et al., 1996). The lack of protective effects from sexual activity with other or multiple partners is also demonstrated by elevated preeclampsia rates in pregnancies achieved with sperm donation (Robillard et al., 1994).

This observation is timely, in light of the discovery that some genes implicated in GWAS studies of schizophrenia are placental genes with differential expression from prenatal adversity (Ursini et al., 2018), which is particularly consistent with preeclampsia and related hypertensive diseases. Prenatal immune activation from preeclampsia could produce lasting inflammatory vulnerability for the mother and fetus, increasing the susceptibility for psychiatric and metabolic conditions. The first report of an overlap between preeclampsia and schizophrenia, in 1954, described subsequent onsets of schizophrenia in women who experienced preeclampsia (Wiedorn, 1954). Likewise, women with mental illness had a 3-fold increase for preeclampsia in a Danish population (Nguyen et al., 2013), although a prior study in that population with a weaker methodology was negative (Bennedsen et al., 2001). A rigorous study found doubled risks for preeclampsia/eclampsia among women with schizophrenia (Vigod et al., 2014), furthermore showing a five-fold increase in death over the post-partum year for women with both disorders. A pooled meta-analysis recently confirmed that preeclampsia was associated with increased risk of offspring schizophrenia, despite some negative studies (Dachew et al., 2018).

This study defined minimal periods of a couple's sexual cohabitation as the duration of their marriage, determined from recorded dates on the marriage and birth certificates. The date they actually commenced

**Table 3**
Categories of paternal age and relative risks for schizophrenia in different models.

| | | | | | | Total |
|---|---|---|---|---|---|---|
| Paternal age (years) | | <25 | 25–34 | 35–44 | 45+ | |
| Schizophrenia | + | 49 | 287 | 175 | 41 | 552 |
| | − | 11,756 | 50,360 | 21,862 | 3845 | 87,823 |
| | | | | | | Trend statistics per 5 years |
| Adjusted for parental psychiatric diagnoses and sex | | | | | | |
| RR | | 1 | 1.17 | 1.60 | 1.87 | 1.34 |
| 95% CL | | Reference | 0.89–1.55 | 1.19–2.15 | 1.20–2.90 | 1.20–1.49 |
| *p* | | | 0.002 | 0.005 | <0.0001 | <0.0001 |
| With additional adjustments for: | | | | | | |
| Only fathers age at marriage | | | | | | |
| RR | | 1 | 1.07 | 1.34 | 1.40 | 1.23 |
| 95% CL | | Reference | 0.80–1.42 | 0.97–1.86 | 0.86–2.29 | 1.08–1.41 |
| *p* | | | 0.66 | 0.08 | 0.17 | 0.002 |
| Only duration of marriage | | | | | | |
| RR | | 1 | 1.25 | 1.88 | 2.21 | 1.47 |
| 95% CL | | Reference | 0.93–1.69 | 1.31–2.70 | 1.37–3.59 | 1.30–1.66 |
| *p* | | | 0.13 | 0.0006 | 0.0013 | <0.0001 |
| Fathers age at marriage and duration of marriage | | | | | | |
| RR | | 1 | 1.09 | 1.42 | 1.51 | 1.38 |
| 95% CL | | Reference | 0.79–1.51 | 0.92–2.19 | 0.84–2.70 | 1.15–1.65 |
| *p* | | | 0.58 | 0.11 | 0.17 | 0.0004 |

sexual contact was not known, however. The risk related to shorter marriage durations occurred at all parental ages. It particularly affected offspring of parents who married at later ages, as they reproduced more quickly after marriage. Their shorter marriages at parturition and paternal age effects explained the risk related to fathers who married at older ages. By contrast, as accounting for parental psychiatric conditions did not influence the risk related to shorter marriages, so it is unlikely that the delay in childbearing by older fathers was due to a genetic behavioral condition. Rather, later childbearing is likely explained by secular reasons.

The risk related to shorter marriages may account for the excess schizophrenia risk identified in firstborn offspring compared to other siblings (Bender et al., 2000; Haukka et al., 2004; Kemppainen et al., 2001) as parents certainly have shorter sexual cohabitation at first births. It is also possible that this effect explains some of the excess risk to offspring of unwanted pregnancies (Herman et al., 2006; McNeil et al., 2009). Risks to later born siblings could reflect a genetic risk, advancing paternal age or other exposures.

The JPSS is uniquely mature, large, prospective population-based birth cohort. Nearly complete follow up of probands and parents was achieved through cross-linkages to national databases maintained by Ministry of the Interior, including a national Psychiatric Cases registry. As some of the parents' diagnoses date back to the 1950s we more broadly defined schizophrenia in parents than offspring and also considered a category of all other psychiatric conditions in the parents. Any misclassification of parents did not influence the findings, however, as the effect of marriage duration remained robust in models that included parental diagnoses.

While marriage duration is not a perfect proxy for the length of the parent's sexual relationship, it is certainly useful as a minimal valid estimate. Israel has among the lowest proportion of extra-marital births, now at 10%, compared to 40% in other countries (the Organisation for Economic Co-operation and Development (OECD), 2018, November 29). Where couples are less likely to wed, defining the date that a relationship had begun may be as valuable, since similar sexual activity is demonstrated for married and cohabiting couples after accounting for other covariates (Schröder and Schmiedeberg, 2015).

Another strength of this study is the use of continuous and stratified analyses to separate the intertwined effects of father's age, his age at marriage and the duration of the marriage for offspring schizophrenia risk, including models that accounted for psychiatric diagnoses in the parents. This partition of risk factors also clarified the robustness of paternal age as an independent risk factor, even for fathers between 25 and 35 years of age, who are relatively young by current standards.

Despite the robustness of exposure to advancing paternal age effect on the risk for offspring schizophrenia, ranging from 1.47, 1.79, 1.95 and 2.70 for fathers aged 30–34, 35–39, 40–44 and 45+ years vs. paternal age <25 years, over 97% of the offspring of the oldest fathers will not have a schizophrenia outcome though this mechanism. This work does clearly demonstrate that paternal age at marriage is not an explanation for the paternal age effect. Paternal age effects were evident even within or the youngest group of fathers when the models were adjusted for the length of marriage, although the exact mechanism for the latter mechanism remains to be defined.

An obvious weakness in the strength of this conclusion is that this work is an epidemiological analysis that did not include intermediary biological measures. There are also other underpinnings for preeclampsia than short coupling durations, including maternal diabetes, hypertension and obesity, a personal or family history of preeclampsia, rheumatoid arthritis or other immune or inflammatory conditions (Vigod et al., 2014).

We propose that accounting for one pathway that operates early in the course of the parental relationship and the other that increases with paternal aging, in addition to family history, may shed light on a large number of conflicting findings in the field. Paternal aging is well supported as a risk pathway related to paternal germ line genetic changes but the pathway linking short duration of marriage to the risk for schizophrenia requires addition research for explication.

The risk from a short period of parental sexual cohabitation may be a modifiable risk factor for offspring schizophrenia risk. The results highlight a novel significant risk factor for fathers related to their duration of sexual contact with the mother prior to conception, which is associated with preeclampsia, proposed to be the linking mechanism. This common condition could underlie the immune activation that is proposed to underlie a central pathology for the disease. After accounting for marriage duration and paternal age, there was no significant risk related to father's age at marriage whereas advancing paternal age remained significantly associated with offspring risk for schizophrenia, apart from genetic susceptibility and other family factors. Accounting for marriage duration and paternal age in addition to family history may illuminate many controversial findings in the epidemiology of schizophrenia.

## Conflicts of interest

All authors declare that they have no conflicts of interest.

### Contributors

The following authors contributed by preserving the original data on which the paper is based: Dolores Malaspina, Karin Rothman, Karine Kleinhaus, Susan Harlap and Yechiel Friedlander.

The following authors verified the accuracy of the figures and conclusions reflecting the data collected: Dolores Malaspina, Caitlin Gilman, Mara Getz, Susan Harlap, Yechiel Friedlander and Thorsten Kranz.

The following authors ensured that the images and statistical analysis are in accordance with Nature journal guidelines: Dolores Malaspina and Sulaima Daboul.

The following authors provided appropriate planning to minimize obstacles to sharing materials, data and algorithms: Dolores Malaspina, Karine Kleinhause, Yechiel Friedlander, Karen Rothman and Mara Getz.

The following authors ensured the overall integrity of the manuscript and data: Dolores Malaspina, Sulaima Daboul, Thorsten Kranz, Judith Weissman, Karine Kleinhaus, Karen Rothman, Caitlin Gilman and Mara Getz.

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