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Age of onset and quality of life among males and females with schizophrenia: A national study

Anat Rotstein*, David Roe, Marc Gelkopf, Stephen Z. Levine

Department of Community Mental Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa 3498838, Israel

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ABSTRACT

Background: Age of onset is considered central to understanding the course of schizophrenia, yet little is known regarding its association with quality of life in general, and specifically among males and females.
Aims: To examine the association between the age of schizophrenia onset and quality of life, in general, and among males and females, using data from a national sample and competing statistical models.
Methods: Participants with a diagnosis of schizophrenia (N = 1624) completed the Manchester Short Assessment of Quality of Life (MSA-QoL) and were rated on a parallel measure by their professional caregivers (N = 578). Multiple regression analysis models were computed for self-appraised quality of life, and mixed models with random intercepts were used for caregivers. Six competing models were tested for parsimony for each rating source. Three models without adjustment and three models adjusted for confounding variables. Sensitivity analyses were conducted for males and females separately.
Results: Age of onset was statistically significantly ($P < .05$) negatively associated with self-appraised and caregiver-appraised quality of life on aggregate and among females. Among males, a significant ($P < .01$) quadratic effect of onset age on self-appraised quality of life demonstrated a negative association up to onset age of 36.67 years, after which the association was positive.
Conclusions: An earlier age of onset is associated with a better quality of life in schizophrenia which is tentatively explained by social decline. Specific trends in psychiatric symptom severity may account for this association among females while social advantages may account for the particular results found among males.

1. Introduction

Age of onset is considered central to understanding the course of schizophrenia [1]. An earlier age of onset is associated with a worse course of the disorder and with poorer outcomes, including a worse course of psychiatric hospitalization in the long and short term [2], poorer educational and vocational adjustment [3], lower levels of social functioning and social cognition [4], and an increased risk of suicide [5].

In contrast with most studies which reported that an earlier age of onset is associated with worse outcomes [2–5], many studies report that age of onset is unrelated to quality of life [6–10], a relevant outcome in schizophrenia [6,11]. Quality of life has developed into a central concept in mental health care [12–15] as treatment goals shifted from symptom change to incorporate recovery outcomes evaluating a personally meaningful life [16,17]. Quality of life and symptom severity only moderately correlated [18–22] and so represent alternative approaches to outcome assessment. One approach views recovery as a subjective process while a contrasting approach defines recovery as an objective outcome [23]. These contrasting approaches may account for the aforementioned particular results of a null association between age of onset and quality of life. Nonetheless, one study reported that early onset mediated associations with quality of life [24], indicating that age of onset played a secondary role in quality of life. Thus a further examination of the role of age of onset on quality of life is needed.

The association between age of onset and quality of life is yet to be explored among males and females. Being female has been previously linked to lower quality of life in schizophrenia [25], while being male has been linked to an earlier onset of schizophrenia [26,27] and poorer outcomes [26,28,29]. These

* Corresponding author.
E-mail addresses: aharshko@campus.haifa.ac.il (A. Rotstein), droe@univ.haifa.ac.il (D. Roe), mgelkopf@univ.haifa.ac.il (M. Gelkopf), slevine@univ.haifa.ac.il (S.Z. Levine).

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aforementioned findings may be accounted for by the distinctive nature of the association between age of onset and quality of life or by specific trends of this association, differentiating males and females.

Research suggests that mental health patients and professional caregivers usually appraise quality of life by relying on different aspects [30–32]. Appraisals by professional caregivers are mostly based on psychiatric symptoms, whereas patients base their appraisals on physical health and social relations [30,31]. Disparities between different rating sources are highly prevalent in studies of quality of life [13,30–,31,32,33,34,35,36]. Hence both self-appraised and caregiver-appraised quality of life scores should be considered for robustness.

The current study aims to examine the association between the age of onset and quality of life, among males and females with schizophrenia, using a national study design with competing statistical models. The current study hypotheses are that age of onset would positively correlate with self-appraised and caregiver-appraised quality of life, and that this correlation would be amplified among males.

2. Methods

2.1. Participants

In this ongoing study, the current cohort was part of the Psychiatric Rehabilitation Routine Outcome Measurement Project [37]. The study was approved by the Helsinki committee at the Ministry of Health and by the Institutional Review Board at the University of Haifa. Assessments were conducted during psychiatric rehabilitation and were supervised by an internal service staff member or externally trained individuals [38].

The current study included a subset of persons with a last diagnosis of schizophrenia who had information on birth year, dates of psychiatric hospital admissions and self and caregiver-appraised quality of life assessments (N = 1624). All participants received national psychiatric rehabilitation services in Israel. The exclusion criteria for psychiatric rehabilitation services are illicit drug addiction, violence and lack of psychiatric monitoring. Participants completed the research questionnaires from January 1st, 2013 to August 19th, 2015. Professional caregivers (N = 578) were given instruments that mirrored the one designed for self-appraisals.

2.2. Data sources

Demographic data (e.g. birth year), hospitalization information (e.g. date and duration of first and subsequent psychiatric hospital admissions) and psychiatric diagnosis were obtained from the Israeli National Psychiatric Case Registry. The registry, established in 1950, contains a lifelong listing of psychiatric hospitalizations in Israel, and includes ICD-10 diagnoses made by an Israeli medical board certified psychiatrist. Registry diagnoses include almost all persons with schizophrenia [39], were found to be reliable over time [40], and have acceptable sensitivity compared to research diagnostic criteria [41]. The registry has been used in numerous studies [2,42,43].

2.3. Quality of life appraisal

Mental health related quality of life was measured and validated [37] based on the Manchester Short Assessment of Quality of Life (MSA-QoL), an abbreviated version of the Lancaster Questionnaire Life Quality Profile [44]. Scale items were rated on a 5-point Likert scale and coded so higher scores on the assessment indicated better quality of life. Eight items measured satisfaction with one's work or volunteering activities, financial status, social status and activities, family relations, leisure activities, residential status, physical health condition and mental health condition (one item per life area). Quality of life appraisals for persons with schizophrenia were made by two rating sources: self-appraised and by their professional caregivers. Caregivers were given an instrument that mirrored the one designed for self-appraisals. The internal reliabilities of the measure were acceptable for self and caregiver-appraisals ($\alpha = 0.76$; $\alpha = 0.77$, respectively).

2.4. Analytic approach

First, descriptive analyses were computed of the sample characteristics. A modest yet statistically significant correlation was observed between self-appraised and caregiver-appraised quality of life ($r = 0.29$, $p < 0.01$), like prior research [30–36]. Mean scores were significantly ($t(1623) = 24.01$, $p < .05$) higher for self-appraisals ($M = 28.86$, $SD = 5.59$) compared to caregiver appraisals ($M = 25.12$, $SD = 4.89$), like prior research [36]. Hence, self-appraised and caregiver-appraised quality of life scores were analyzed for robustness.

Second, the primary statistical analysis examined the association between self-appraised and then caregiver-appraised quality of life as a function of age of onset using regression models. The assumptions of the regression models were tested. Visual inspection of residual figures was performed in order to reveal deviations from homoscedasticity or normality. An inspection for normality of error terms followed using a histogram and probability plots of the residuals. Independence of the error term was examined through a scatter plot of residuals by the predicted values to show that no discernible association existed. Then, statistically significant outliers were removed as their inclusion offsets estimation [45]. Next, multiple regression analysis models were computed for self-appraised quality of life. Mixed models with random intercepts for caregivers were then used to account for the repeated caregiver ratings in the data. Significance for mixed regression models was calculated by comparing models via the likelihood ratio test.

Competing models for each rating source were computed in ascending complexity and tested without adjustment and adjusted for confounding of birth year, age at the time of data collection, duration of disorder and whether male or female. The age of onset was derived from the difference between the date of birth and date of first psychiatric hospital admission. Duration of disorder was derived from the difference between the time of data collection and the date of first psychiatric hospital admission and was categorized into four categories cased on quartile scores. Age at the time of data collection was derived from the difference between the time of data collection and the date of birth and was categorized into two categories based on the median score. Birth year was categorized into two categories based on the median score. Models for each rating source were numbered as follows. The first model accounted for a linear effect of age of onset on self-appraised quality of life (model 1 hereafter). The second model accounted for a linear effect of age of onset, whether male or female, birth year, age at the time of data collection and duration of disorder (model 2 hereafter). The third model accounted for a quadratic effect of age of onset on self-appraised quality of life (model 3 hereafter). The fourth model accounted for a quadratic effect of age of onset, whether male or female, birth year, age at the time of data collection and duration of disorder (model 4 hereafter). The fifth model accounted for a cubic effect of age of onset on self-appraised quality of life (model 5 hereafter). The sixth model accounted for a cubic effect of age of onset, whether male or female, birth year, age at the time of data collection and duration of disorder (model 6 hereafter).

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Third, models for each rating source were compared for parsimony based on the Bayesian Information Criterion (BIC) for model selection [46], similar to prior research [47,48]. Lower BIC values represent more parsimonious models and so are a better fit to the data.

In instances of quadratic models, the cutoff point was computed by setting the second derivative equal to zero [49]. Since an upward concave corresponds to a positive second derivative and downward concave corresponds to a negative second derivative, then when the function changes from upward concave to downward concave (or vice-versa) the second derivative equals to zero.

Sensitivity analyses were conducted for males and females, like in prior research [2]. All regression models were recomputed separately for males and females and then compared for parsimony.

All analyses were computed in R [50] with the lme4 library [51] used to compute linear mixed effects of the associations between caregiver-appraised quality of life and age of onset.

3. Results

3.1. Sample characteristics

The final sample was based on 1551 persons with schizophrenia rated by 564 professional caregivers. This sample size was a result of removing all outliers (N = 73, 4.5%). Of the remainder a total of 62% (N = 957) of the participants were males (N = 594 females). Overall mean age for first psychiatric hospital admission was 25.55 years (SD = 8.32), 26.13 years (SD = 8.91) for females, and 25.18 years (SD = 7.92) for males. Overall mean birth year was 1967 (SD = 12.03 years; mean age at time of data collection was 46.5 years), for females 1966 (SD = 12.13 years; mean age at time of data collection was 47.84 years), and for males 1968 (SD = 11.90 years; mean age at time of data collection was 45.66 years). Overall mean duration of disorder was 21.05 years (SD = 11.72), 21.81 years (SD = 12.02) for females, and 20.58 years (SD = 11.52) for males. See Table 1 for mean and 95% confidence interval values of quality of life appraisals and age of onset.

Among the caregivers, 44% (N = 249) appraised one person with schizophrenia, 21% (N = 120) appraised two persons, 11% (N = 61) appraised three persons, and 24% (N = 134) appraised four or more persons.

3.2. Primary statistical analysis

3.2.1. Self-appraised quality of life as a function of age of onset

Comparison of the six competing regression models showed that model 1 was the most parsimonious (BIC = 9573.99; Table 2; See Table 3 for comparison of BIC values for all self-appraised quality of life models). This model indicated that age of onset alone was significantly (P < .01) negatively associated with self-appraised quality of life (Fig. 1a).

Table 1
Mean and 95% confidence interval values of quality of life and age of onset.

	Total Sample N = 1551	Females N = 594	Males N = 957
	Age of Onset		
Mean (SD)	25.55 (8.32)	26.13 (8.91)	25.18 (7.92)
95% confidence interval values	25.13, 25.96	25.41, 26.85	24.68, 25.69
	Self-appraised quality of life		
Mean (SD)	28.85 (5.59)	28.56 (5.63)	29.03 (5.56)
95% confidence interval values	28.57, 29.13	28.11, 29.01	28.68, 29.38
	Caregiver-appraised quality of life		
Mean (SD)	25.08 (4.88)	24.96 (4.96)	25.15 (4.82)
95% confidence interval values	24.83, 25.32	24.56, 25.37	24.84, 25.45

Table 2
Best-fitting quality of life model parameters.

Model	Estimates	SE	T	P	BIC
Self-appraised quality of life models					
Model 1: Intercept	30.33	0.46	66.53	<0.01	9573.99
Age of Onset	−0.06	0.02	−3.40	<0.01	
Model 1- F : Intercept	30.29	0.71	42.46	<0.01	3750.57
Age of Onset	−0.07	0.03	−2.56	0.01	
Model 3- M: Intercept	35.35	1.85	19.06	<0.01	6012.84
Age of Onset	−0.44	0.14	−3.20	<0.01	
Quadratic Age of Onset	0.01	0.002	2.88	<0.01	
Caregiver-appraised quality of life models					
Model 1 : Intercept	25.82	0.40	64.13	<0.01	9291.33
Age of Onset	−0.03	0.01	−2.11	0.04	
Model 1- F : Intercept	26.30	0.64	41.35	<0.01	3607.00
Age of Onset	−0.05	0.02	−2.40	0.02	

Self-appraised quality of life models:
Model 1: Self-appraised quality of life = Intercept + Age of Onset.
Model 1- F: Female self-appraised quality of life = Intercept + Female Age of Onset.
Model 3- M: Male self-appraised quality of life = Intercept + Male Age of Onset + (Male Age of Onset)^2.
Caregiver-appraised quality of life models:
Model 1: Caregiver-appraised quality of life = Intercept + Age of Onset.
Model 1- F: Caregiver-appraised female quality of life = Intercept + Female Age of Onset.

3.2.2. Caregiver-appraised quality of life as a function of age of onset

Comparison of the six competing linear mixed effect models showed that model 1 was the most parsimonious (BIC = 9291.33; Table 2; See Table 3 for comparison of BIC values for all caregiver-appraised quality of life models). This model accounted for a linear effect of age of onset on caregiver-appraised quality of life, beyond the effect of each individual caregiver (Fig. 2a) and indicated that age of onset alone was significantly (P < .05) negatively associated with caregiver-appraised quality of life.

3.3. Sensitivity analysis: age of onset and quality of life among males and females

All aforementioned models were recomputed separately for males and females (see Table 3 for BIC values). Consistent with the results of the primary analysis, among females with schizophrenia, for self-appraised quality of life, model 1 (a linear effect of age of onset on self-appraised quality of life) was the best fitting model (BIC = 3750.57; Table 2; Fig. 1b). Among males with schizophrenia, model 3 was the best fitting model (BIC = 6012.84; Table 2; Fig. 1c). Model 3 consisted of a quadratic effect of age of onset alone on self-appraised quality of life, inconsistent with the linear effect found for the total sample. This model had an inflection point, in which the curve changed from being concave downward to being concave upward, at onset age of 36.67 years.

The unique effects of males and females were also found for the mixed models (see Table 3 for BIC values). Consistent with the primary analysis, among females with schizophrenia, for caregiver-appraised quality of life, model 1 (a linear effect of age of onset beyond the effect of individual caregivers, on caregivers' appraisals of quality of life) was the best fitting model (BIC = 3607.00; Table 2; Fig. 2b). Among males with schizophrenia, age of onset could not significantly predict caregiver-appraised quality of life, using any of the mixed models described (see Fig. 2c), a result which was inconsistent with the linear effect found for the total sample.

4. Discussion

The current study examined the association between the age of onset and quality of life, among males and females with schizophrenia, using data from a national sample and competing

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Table 3
BIC values for self-appraised and caregiver-appraised quality of life models.

Models compared	Total sample self-appraised quality of life BIC	Female sample self-appraised quality of life BIC	Male sample self-appraised quality of life BIC
Model 1	9749.41	3750.57	6014.24
Model 2	9775.76	3768.26	6034.66
Model 3	9753.80	3756.83	6012.84
Model 4	9779.71	3774.45	6032.83
Model 5	9760.86	3763.18	6019.69
Model 6	9786.77	3780.77	6039.68

Models compared	Total sample caregiver-appraised quality of life BIC	Female sample caregiver-appraised quality of life BIC	Male sample caregiver-appraised quality of life BIC
Model 1	9291.33	3607.00	5727.19
Model 2	9304.84	3618.23	5737.30
Model 3	9307.77	3623.15	5743.99
Model 4	9321.75	3634.64	5754.30
Model 5	9330.68	3644.07	5766.00
Model 6	9344.80	3655.64	5776.32

Note: The lowest BIC is the best-fitting model and is underlined for clarity.
Self-appraised quality of life models:
Model 1: Self-appraised Quality of Life = Intercept + Age of Onset.
Model 2: Self-appraised Quality of Life = Intercept + Age of Onset + Birth year + Duration of disorder + Age.
Model 3: Self-appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$.
Model 4: Self-appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + Birth year + Duration of disorder + Age.
Model 5: Self-appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + $(\text{Age of Onset})^3$.
Model 6: Self-appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + $(\text{Age of Onset})^3$ + Birth year + Duration of disorder + Age.
Model 2, model 4 and model 6 for the total sample were also adjusted for being male or female.
Caregiver-appraised quality of life models:
Model 1: Caregiver-appraised Quality of Life = Intercept + Age of Onset.
Model 2: Caregiver -appraised Quality of Life = Intercept + Age of Onset + Birth year + Duration of disorder + Age.
Model 3: Caregiver -appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$.
Model 4: Caregiver -appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + Birth year + Duration of disorder + Age.
Model 5: Caregiver -appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + $(\text{Age of Onset})^3$.
Model 6: Caregiver -appraised Quality of Life = Intercept + Age of Onset + $(\text{Age of Onset})^2$ + $(\text{Age of Onset})^3$ + Birth year + Duration of disorder + Age.
Model 2, model 4 and model 6 for the total sample were also adjusted for being male or female.

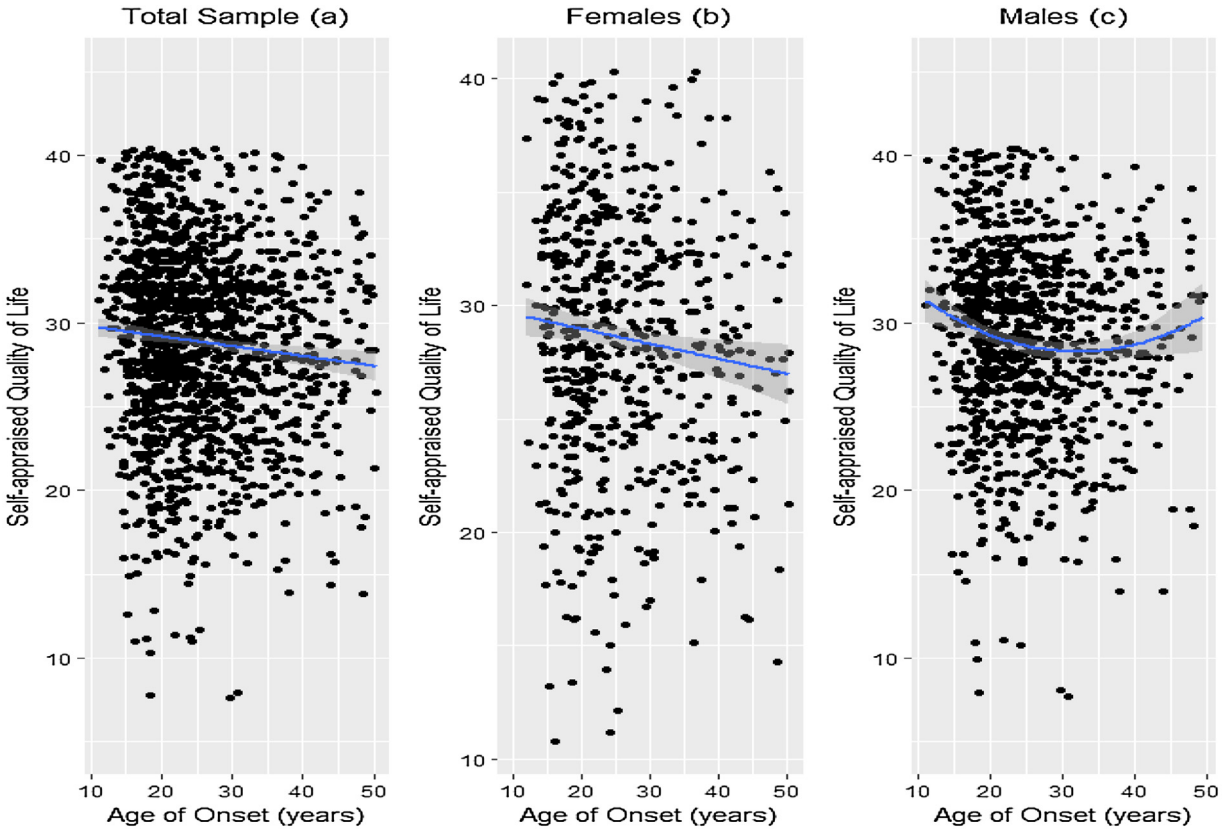

Fig. 1. Self-appraised quality of life as a function of age of onset.
Note: The slope in figure 1a is based on Model 1 (Self-appraised quality of life = Intercept + Age of Onset).
The slope in figure 1b is based on Model 1 for females (Self-appraised female quality of life = Intercept + Female Age of Onset).
The slope in figure 1c is based on Model 3 for males (Self-appraised male quality of life = Intercept + Male Age of Onset + (Male Age of Onset)^2.

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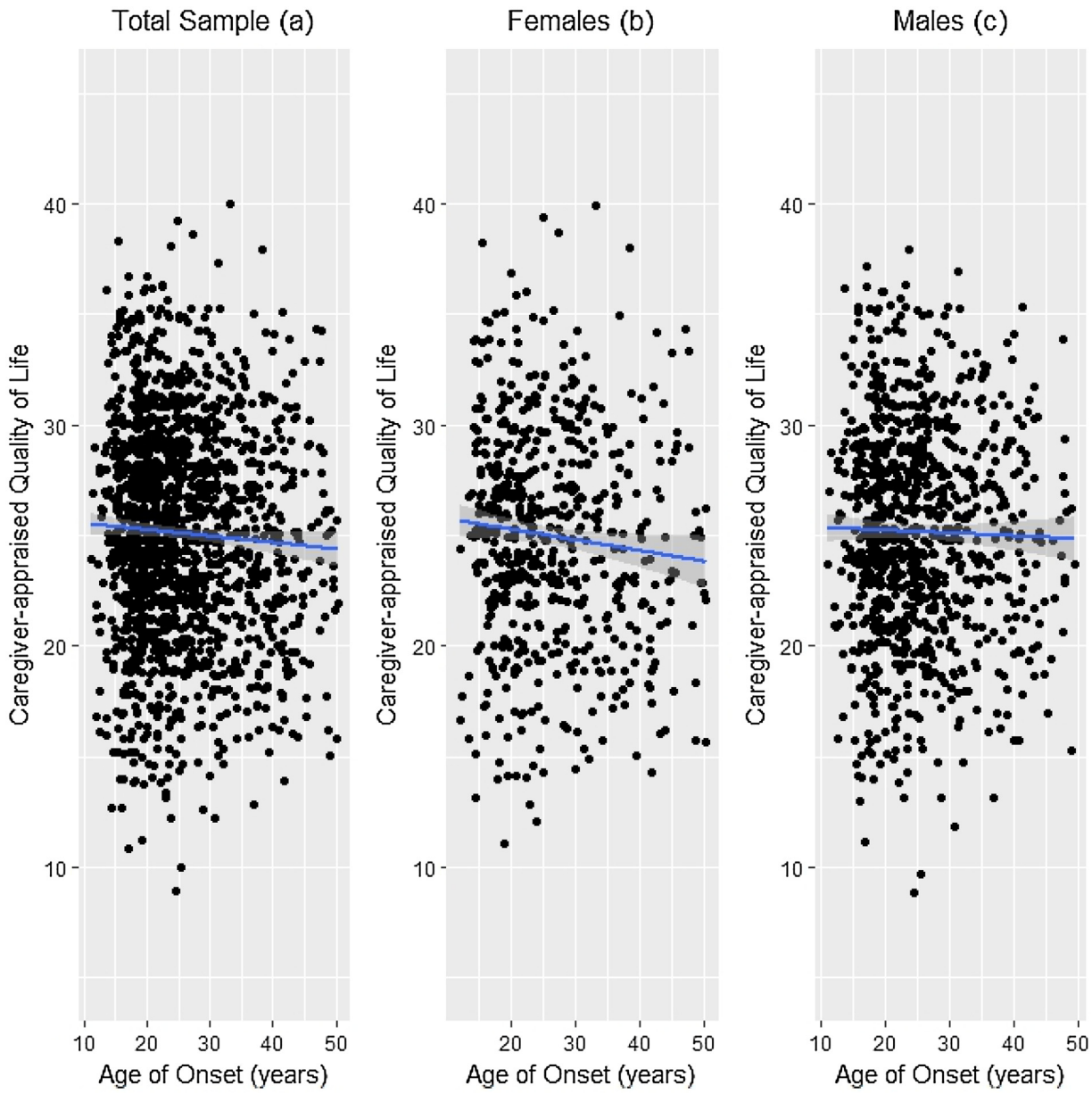

Fig. 2. Caregiver-appraised quality of life as a function of age of onset.
Note: *The slope in figure 2a is based on Model 1* (*Caregiver-appraised quality of life = Intercept + Age of Onset*).
The slope in figure 2b is based on Model 1 for females (*Caregiver-appraised female quality of life = Intercept Female Age of Onset*).
Figure 2c presents a non-significant slope since for males, age of onset was not statistically significantly associated with caregiver-appraised quality of life using any of the mixed models computed.

statistical models. Results show that self-appraised or caregiver-appraised quality of life decreased as age of onset increased, contrary to the study hypothesis of a positive correlation.

The current study result that age of onset is negatively associated with quality of life in schizophrenia, may seem incongruent with much research claiming that earlier onset age is associated with poorer outcomes [2]. Nonetheless, quality of life differs in its experience [6] compared to the other outcomes (e.g., the course of psychiatric hospitalizations) that have been examined for their association with age of onset. Taken together with prior research, social decline may tentatively explain the reported tendency to generally appraise lower quality of life as the age of onset increases [52–56].

Similarly, the current findings show that for females with schizophrenia, quality of life appraisals decreased as the age of onset increased. Some earlier evidence suggests that a unique trend for females may be accounted for by psychiatric symptom severity. Late-onset females with schizophrenia (but not males) were found to have a general negative symptoms score more unfavorable than early-onset females [53,57], perhaps due to a reduced protective effect of estrogen [54]. Psychiatric symptoms were steadily found to be negatively related to quality of life (see meta-analysis (18)) and their severity may tentatively explain the progressing decrease in female quality of life.

Finally, among males, results showed a quadratic effect of onset age on self-appraised quality of life, contrary to the study hypothesis that the positive correlation between onset age and quality of life would be amplified. The quadratic effect demonstrated a negative association up to onset age of 36.67 years, after which the association was positive. The age of 36 has been

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observed to distinguish early and late onset [58] and confer to a reduced risk of suicide, especially for males [59]. The positive association between age of onset and quality of life among males after the age of 36.67 may reflect the higher chances of retaining acquired social advantages associated with later onset [53]. Male onset age was not associated with caregiver-appraised quality of life, suggesting that the association is not robust like previously discussed, and that disparities between different rating sources largely exist for males.

5. Limitations

The current results are based on an abridged version of the MANSA [44]. More recent and broader quality of life measures exist that may yield different trends. Further, the underlying concept of quality of life in this questionnaire is generic and not disorder-specific. The measure, however, was chosen for pragmatic reasons of time and administration to a large sample [60]. Additionally, although past studies suggest that information from patients is no less valid than data from other sources [61], the current data consist of two quality of life rating sources which enable greater confidence than had a single data source been used. Finally, quality of life was appraised by different sources than those from which onset age was derived, and there was a difference of 21.05 years (on average, SD = 11.72) between the actual age of onset and the time of assessment completion. Still, future research is warranted to ensure that the results generalize to other tools and samples.

Other than date of first psychiatric hospital admission, different age of onset measures, such as age when behavioral changes begin to occur or age at first manifestation of positive symptoms (e.g.(1)), were not available. However, past research indicates that there is close correspondence between different onset definitions [62,63].

Furthermore, a longer duration of untreated psychosis, which was not measured in the current study, cannot be ruled out as an explanation of the association found in this study. Indeed, other research has reported a moderate yet significant correlation between duration of untreated psychosis and onset age [64,65].

Similarly, the current study did not consist of information on the psychiatric symptoms of schizophrenia disorder (e.g., the PANSS [66]) and specifically on negative symptoms which were found integral to quality of life [53,57]. We were therefore unable to learn of the actual interplay between symptoms, age of onset and quality of life, among males and females. Future studies may look into these associations.

6. Summary

This is the first study to examine competing statistical models of the association between quality of life appraisals and age of onset using a national study design. Age of onset was significantly associated with quality of life in schizophrenia, whether self-appraised or caregiver-appraised, and this association differed among males and females. Quality of life appraisals decreased as the age of onset increased for the general sample and for females. For males, a quadratic association was found between age of onset and self-appraised quality of life. Results may be tentatively explained by mechanisms of social decline, social advantages and symptomatology.

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Conflict of interest

None. The authors report no conflict of interest in the past three years and are responsible for the content and writing of the paper.

Contributors

Author Anat Rotstein wrote the publication study protocol, managed the literature searches, conducted the statistical analysis and wrote the first draft of the manuscript. Authors Anat Rotstein and SZL designed the publication study protocol. All authors provided critical statistical and manuscript feedback. All authors contributed to and approved the final manuscript.

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