Title: The predictive power of expressed emotion and its components in relapse of Schizophrenia: A meta-analysis and meta-regression

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Abstract

Background. Schizophrenia is a longstanding condition and most patients experience multiple relapse in the course of the condition. High expressed emotion (HEE) has been found to be a predictor of relapse. This meta-analysis and meta-regression examined the association of global EE and relapse specifically focusing on timing of relapse and EE domains.

Methods. Random-effects model was used to pool the effect estimates. Multiple random-effects meta-regression was used to compute the moderator analysis. Putative effect moderators including culture, EE measurements, age, length of condition and study quality were included.

Results. Thirty-three prospective cohort studies comprising 2284 patients were included in the descriptive review and 30 studies were included for meta-analysis and meta-regression. Findings revealed that global HEE significantly predicted more on early relapse (≤ 12 months) (OR, 4.87 [95% CI, 3.22–7.36]) than that on late relapse (> 12 months) (OR, 2.13 [95% CI, 1.36–3.35]). Higher level of critical comments (CC) significantly predicted relapse (OR, 2.22 [95% CI, 1.16–4.26]), whereas higher level of warmth significantly protected patients from relapse (OR, 0.35 [95% CI 0.15–0.85]). None of the moderators included significantly change the results.

Conclusions. These findings indicate that there is a dynamic interaction between EE-relapse association with time, and CC and warmth are the two important EE domains to influence relapse among patients with schizophrenia. Results also confirmed the foci of family interventions on reducing critical comments and improving warmth in relationship.

Key words: Express emotion, family caregiver, psychosis, relapse

Introduction

Schizophrenia is a longstanding condition affecting 1% of the population with the majority of patients experiencing multiple relapses during the course of the condition (Emsley, Chiliza, Asmal, & Harvey, 2013; Rössler, Salize, Os, & Riecher-Rossler, 2005), and most relapses tend to occur during the early stage of the condition (Chan et al., 2015; Hui et al., 2013). Relapses have a significant impact on the outcomes of patients. Studies have shown that early relapses are associated with increase suicide mortality (Chan et al., 2018) and poor long-term trajectories of employment (Chen et al., 2020). About 1 in 6 patients was found to exhibit protracted impairment after relapse (Emsley et al., 2013). Longitudinal neuroimaging studies further provide evidence on the neuro-deterioration associated with relapse (Andreasen, Liu, Ziebell, Vora, & Ho, 2013; van Haren et al., 2007). Relapses also carry a significant economic burden to the society (Pennington & McCrone, 2017). Therefore, identification of risk factors of relapse and providing effective relapse prevention intervention are critical to the long-term management of patients with schizophrenia.

Many studies have reported demographic and clinical related risk factors of relapses in patients with schizophrenia. These include medication non-adherence (Alvarez-Jimenez et al., 2017), smoking (Hui et al., 2013), older paternal age (Hui et al., 2015), and cognitive functions such as visual working memory (Hui et al., 2016). Despite medication non-adherence has been found to be the most significant clinical predictors of relapse (Caseiro et al., 2012), about 50% of patients relapsed while having good adherence to medication (Linszen et al., 1997). Environmental, particularly family related factors, is also important. One factor that has been examined extensively is caregiver expressed emotion (EE). The construct of EE was developed in the 1950s and it comprised four domains: critical comments (CC), hostility, emotional overinvolvement (EOI), and warmth (Amaresha & Venkatasubramanian, 2012; Hooley & Parker, 2006). The role of caregiver or family EE in predicting patient relapse has been reported in many studies and has been suggested as a major predictor of relapse in both patients with first-episode and longstanding conditions in an early study (Linszen et al., 1997).

An earlier meta-analysis study concluded that high EE is associated with approximately one third of relapses in patients with schizophrenia (Butzlaff & Hooley, 1998), and appears to be more prominent in patients with longstanding schizophrenia. As cultural variation may be contributed to the degree and manifestation of the EE domains, and there is a possible differential association between EE and relapse with different culture (Kopelowicz et al.,

2002), a more recent meta-analysis specifically look into the cross-cultural effect of the relationship between EE and relapse. The study, however, revealed no significant cultural variation of EE and the link between EE and relapse appeared to be universal among population of different culture (O'Driscoll, Sener, Angmark, & Shaikh, 2019). This result is similar to the earlier meta-analytic study with much less studies included, that is no regional differences were found (Butzlaff & Hooley, 1998). However, both of these reviews suffered from some limitations. Methodologically, these meta-analyses included a noticeable amount of experimental studies that restricted the pooled effect estimation. The power issue of the included studies as well as attrition bias were not considered, and their findings on the moderators of the EE-relapse association were inconsistent. Furthermore, only studies using Camberwell Family Interview (CFI) (Vaugh & Leff, 1976) as EE measurement were considered without taking consideration of studies using other valid EE instruments such as Five-minute Speech Sample (FMSS) (Magana et al., 1986), and Level of Expressed Emotion Scale (LEES) (Cole & Kazarian, 1998). The understanding of specific roles of the individual domains of EE in relationship with relapse and time of relapse could inform the development of future intervention and yet this was not explored.

In order to fill these research gaps and overcome the limitations of previous reviews, we systematically evaluate the literature to examine the global EE-relapse association by timing of relapse, EE domain-relapse association, and its putative effect moderators. Studies with all valid EE measures were included. Results of this meta-analysis can provide comprehensive understanding of the relationship between EE and relapse in patients with schizophrenia, and inform the development of family-focused intervention.

Methods

Search strategy

Potential research articles, grey literatures, and ongoing studies were identified from eight databases including Web of Science Core Collection (1956–2020), PsycINFO (1806–2020), MEDLINE (1946–2020), EMBASE (1947–2020), CENTRAL (1908–2020), CNKI (1984–2020), Airiti Library (1991–2020), ProQuest Dissertation & These A&I (1743–2020), and two trial registries, ClinicalTrials.gov (1997–2020) and ICTRP (2004–2020). The prespecified search terms used were (expressed emotion OR EE OR emotional over involvement OR EOI OR hostile OR hostility OR critical comments OR criticism OR warmth OR positive regards

OR Camberwell Family Interview OR CFI) AND ti(relapse OR readmission OR rehospitali?ation OR exacerbation OR course) AND ti(schizophrenia OR schizo* OR psychosis OR psychotic OR psychiatric). The search was conducted from the inception dates of the databases to May 2020 and it was limited to English and Chinese languages. We also searched the bibliography of the identified articles for more eligible research. This review was prospectively registered in PROSPERO (CRD42020173218) and was reported in line with the PRISMA checklist (Moher et al, 2009).

Inclusion and exclusion criteria

We used the PEO framework to screen and select the eligible studies (Moola et al., 2017). Studies with at least half of the patients diagnosed with schizophrenia-spectrum disorders using any valid diagnostic methods and are living or in close contact with families were included. The included studies used any valid EE measurements that allowed categorisation of the population into high EE (HEE) or low EE (LEE), and relapse events of patients in a specific time frame by EE groups were reported. In addition, we included prospective cohort studies, while experimental studies were excluded to prevent the pooled effect estimate being contaminated by the treatment allocation.

Data extraction and management

Two researchers (CFM & YLC) independently conducted the systematic literature search. All identified studies were cross-checked and consensus was reached for any disagreement. Important study characteristics, including study geographical location, number of subjects, patients' age, length of condition, EE measures, relapse measures, time of follow-up, attrition rate, number of relapse, and study methodological quality, were extracted and tabulated. If length of condition was not readily available in the report, the number of prior hospitalisations was used instead. Patients with less than five years of onset or three prior hospitalisations would be categorised into recent-onset group, while the remaining would be categorised into longstanding type (Butzlaff & Hooley, 1998). Attrition rate was calculated as the loss of follow-up of the original recruited sample. Relapse events were extracted according to the operational definition of relapse in the respective studies. Besides, timing of relapse was divided into early relapse and late relapse. Early relapse referred to relapse occurred on or before twelve-month follow-up, while late relapse referred to relapse occurred after twelve-month follow-up. Data extracted was cross checked by the two researchers.

Risk of bias (RoB) assessment

Two researchers (CFM & YLC) independently carried out the bias assessment. The results were cross-checked and consensus was reached for any disagreement. Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies was used to assess the risk of bias across the studies (Moola et al., 2017). This eleven-item scale addresses the selection bias, information bias, misclassification bias, confounding control measures and other important methodological issues. In parallel, STROBE Statement was used to complement the overall bias assessment (vom Elm et al., 2007). Overall low, moderate, and high RoB was determined for each study to categorise the methodological quality across studies. We graded studies with small sample size (i.e. $N < 60$) or high attrition rate (i.e. > 20%) without appropriate imputation methods as having moderate RoB, because of the possible presence of Type II error (Akl et al., 2012).

Putative moderators

Apart from the covariates reported in the previous meta-analyses including the length of condition, study geographical location and time of study, other factors including patients' age, culture, EE measures, proportion of schizophrenia sample, and study quality were also added as covariates in the moderator analysis of the current study. Culture was broadly grouped into Western and Eastern culture (Dwairy & Achoui, 2010a; Dwairy & Achoui, 2010b). EE measures were categorised into CFI and other validated instruments (non-CFI). Study quality was grouped into low, moderate, and high RoB. Publication year was divided into two groups using publication year of 1998 as a cutoff as this was the publication year of the first meta-analysis of impact of EE on relapse of patients with schizophrenia (Butzlaff & Hooley, 1998).

Statistical analysis

Spearman correlation test was used to examine the relationship between study methodological quality, attrition rate and publication year. In the meta-analysis, we used random-effects model with inverse-variance weighting method to pool the effect estimates in odds ratio (OR) and 95% confidence interval (CI), as the studies were heterogeneous in terms of sociodemographic factors and selection of the outcome measures. Since random-effects model would unavoidably add more weight to the small studies, sensitivity analyses were conducted on the overall pooled effect estimate by removing the small studies and studies with high RoB. In addition, the pooled effect estimates by follow-up period and EE subscales was further analysed. EE subscales consisted of CC, EOI, hostility, and warmth. Multiple random-effects meta-

regression was conducted to examine the association between study characteristics and the effect estimates. Odds ratio (OR) and 95% CI were imputed by anti-logging the β and the product of 1.96 and standard error (Bland & Altman, 2000). Leave-one-out sensitivity analysis and cumulative analysis by chronological order were performed to ensure the stability of pooled effect estimates from individual studies and across publication periods respectively. Lastly, to examine the publication bias or small-study effect for pooled dichotomous outcomes with between-study variances, tau-squared (τ^2) > .01, funnel plot followed by arcsine test and trim-and-fill procedure were conducted (Higgins et al., 2020; Rucker, Schwarzer, & Carpenter, 2008).

R Studio version 1.3.959 (RStudio Team, 2020), RevMan version 5.3 (Review Manager, 2014), and Open Meta-analyst version 12.11.14 (OpenMetaAnalyst, 2014) were used to carry out statistical inference and produce graphs including forest plots and funnel plot. With-in study and between-study variances could be observed by the CI width and tau-squared (τ^2), while study heterogeneity and subgroup difference were determined if p was < .05 in Chi-squared (χ^2) test and I-squared (I^2) was greater than fifty percentages (Higgins et al., 2020). To avoid Type I error caused by multiple testing, the null hypothesis in moderator analysis was rejected if both p values from Omnibus test and regression were smaller than .05.

Results

Study selection

The search was conducted between 1st April 2020 and 31st May 2020. PRISMA diagram (Fig. 1) shows the study selection process. Thirty-three studies comprising thirty-eight research reports were identified and included in descriptive synthesis, while thirty studies were meta-analysed/meta-regressed on the relapse outcome and effect moderators. Three studies were excluded from the meta-analysis because the authors did not report relapse events and/or the relapse events could not be imputed and pooled. Nineteen studies were excluded due to reasons including not cohort design (k = 14), < 50% patients diagnosed with schizophrenia (k = 2), < 50% patients living with families (k = 2), and patients comorbid with substance abuse (k = 1).

Sample and study characteristics

Table 1 summarised the characteristics of included studies. In total, 2284 patients participated in the 33 studies from 21 countries. There were 61.7% male (k = 29, N = 1175) and 55.5 % of

the patients were unemployed (k = 7, N = 253) with mean age of 30.8 (k = 27, SD = 6.5, range = 16.4–39.0). 54.5% studies recruited patients with longstanding condition (k = 18), 66.7% studies were from Western countries (k = 22) and nearly half of these were from UK (k = 5) and US (k = 5). The mean sample size was 69.2 (SD = 28.5, range = 15–134). The average follow-up duration was over a year (mean = 15.5 months, SD = 13.8, range = 6–84), and the attrition rate was sizable (mean = 11.3%, SD = 11.6%, range = 0%–39.7%). Twenty-six (78.8%) studies used CFI as the EE measure, while relapse measures varied among studies with four main approach including using valid instruments, clinical consultation, rehospitalisation, or mixture of these, in which 15.2% of the studies (k = 5) adopted rehospitalisation as the only relapse indicator.

EE and overall relapse rate

The weighted mean of HEE family members of people with schizophrenia across studies was 50.9% (SD = 12.5) (k = 30, N = 1853, range = 23.3%–76.2%), in which CC (k = 14, N = 893, mean = 46.9%, SD = 18.3, range = 25.0%–94.1%), hostility (k = 5, N = 238, mean = 48.9%, SD = 32.1, range = 19.3%–80.0%), and EOI (k = 14, N = 893, mean = 36.3%, SD = 17.6, range = 12.0%–72.2%) were the three most reported EE among the four domains. By culture, Western countries had significantly more HEE families (k = 21, N = 1261, mean = 55.5%, SD = 11.4) than that of Eastern countries (k = 9, N = 592, mean = 41.1%, SD = 9.12, $p < .00001$), and it was similar for the CC subscale (p = .06). The overall relapse rate of all participants across different time points of follow-ups was large (k = 30, mean = 43.7%, SD = 12.7, range = 15.8–73.3%).

Meta-analysis findings: Relapse prediction by global EE

Significant relation was found between HEE and relapse (k = 30, N = 1853, OR, 3.74 [95% CI, 2.75–5.09]) (Fig. 2). The subgroup analysis of timing of relapse found HEE had a significant effect on early relapse (k = 20, N = 1237, OR, 4.90 [95% CI, 3.46–6.94] and late relapse (k = 10, N = 616, OR, 2.09 [95% CI, 1.40–3.13] (Fig. 2). The differences of the effects on early and late relapse was also significant (χ^2 = 9.82, p = .002, I^2 = 89.8%). When six studies with high RoB were removed, the effect estimates on overall (OR, 3.67 [95% CI, 2.58–5.22]), early relapse (OR, 4.87 [95% CI, 3.22–7.36]), late relapse (OR, 2.13 [95% CI, 1.36–3.35], and subgroup difference by timing of relapse were still significant (χ^2 = 6.99, p = .008, I^2 = 85.7%). Similarly, when another six studies that was considered as extreme outliers (i.e. OR > 40) were removed, the effect estimates on overall (OR, 3.21 [95% CI, 2.37–4.34]), early relapse (OR,

4.17 [95% CI, 2.94–5.93]), late relapse (OR, 2.02 [95% CI, 1.36–2.98]), and subgroup difference remained significant (χ^2 = 7.33, p = .007, I^2 = 86.4%). However, when focusing on the parental EE-relapse association, in which studies explicitly reported that at least eighty percent of the family members were parents, the pooled effect estimate dropped from 3.74 to 2.73 (k = 10, N = 506, OR, 2.73 [95% CI, 1.35–5.56], p = .005).

Meta-analysis findings: Relapse prediction by EE domains

Higher CC (k = 10, N = 717, OR, 2.22 [95% CI, 1.16–4.26]) was significantly related to more relapse while higher level of warmth (k = 2, N = 116, OR, 0.35 [95% CI, 0.15–0.85]) was related to lower relapse rate (Fig. 3). Other domains of EE were not found to have significant relationship with relapse. After removing two studies with high RoB, only CC had a trend significance in relating with relapse (k = 8, N = 621, OR, 1.82 [95% CI, 0.94–3.52], p = .08).

Factors affecting EE-relapse association

Categorical moderator analysis was computed to examine the seven putative moderators including age, proportion of schizophrenia sample, length of condition, culture, EE measures, RoB, and publication year (Table 2). None of them was significantly associated with EE-relapse linkage (p = .83), and the findings remained the same by changing some of the variables into continuous data such as length of condition and publication year. After removing six high RoB studies, the results of moderator analyses also remained similar (p = .82).

Study methodological rigor

Supplementary Table 1 described the results of bias assessment and the breakdown evaluation of the eleven-item Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies. Thirty-one (81.6%) research reports were graded as low-moderate RoB and the included studies were found to be susceptible to selection bias, attrition bias, and reporting bias. Twenty-nine (76.3%) studies did not explicitly report assessment of the covariates and its influence on the effect estimates by using appropriate statistical methods. Almost all studies used complete case analysis to treat the loss of follow-up, but only 21.1% of these studies (k = 8) met the analysis assumption. Moreover, two studies with an average 17.8% attrition rate did not explicitly describe the reasons of loss of follow-up. Only two studies reported the sample size calculation and one-third of the studies (k = 11) recruited samples of less than 60. Besides, the study methodological quality improved with time (ρ = 0.38, p = .03) and negatively correlated

with attrition rate (ρ = –0.69, p = .0000081). However, no significant association was found between study methodological quality and the effect estimate (Table 2).

Leave-one-out analysis revealed that the pooled effect estimate remained stable after removing any one of the studies one at a time (Supplementary Fig. 1). The pooled OR and the percentage changes from the baseline ranged from 3.60 (–3.74%) to 3.96 (5.88%). Cumulative analysis (Supplementary Fig. 2) by publication year indicated that the pooled effect estimate became stable since 1992. Besides, although there were a few missing dots in the lower left quadrant in the funnel plot (Supplementary Fig. 3), publication bias did not exist. It was confirmed by arcsine test (p = .25) and this concern might be caused by the small-study effect (Sterne et al., 2011). Trim-and-fill method suggested that the bias-adjusted overall OR was 3.28 (95% CI, 2.39–4.49), similar to the effect estimates after removing the six small studies mentioned in the previous paragraph.

Discussion

This meta-analysis and meta-regression study critically appraised and examined the existing evidence to provide a comprehensive overview of EE-relapse association in schizophrenia. Global HEE was significantly related to relapse, more with early relapse (within 12 months) than the late relapse. Of the four domains of EE, CC predicted relapse and warmth had protective effects. Age, length of condition, culture, EE measurements and publication years did not significantly moderate the outcome. This review also found Western studies reported more HEE families than that from the Eastern regions.

Only cohort studies were included in the current study to minimise selection and attrition biases. We found a significant relationship between global EE and relapse, that is consistent with the previous meta-analyses result, further highlighting the significance of the EE of caregivers in relapse prevention. In exploring more comprehensively the EE-relapse relationship, the current studies provided several new findings. First, we found high EE associated with early relapse more significantly than the later relapse. This suggested a dynamic interaction between EE and relapse with time. As there are multiple factors contributing to the risk of relapse, change of factors including EE with time might impact on the relationship of EE and relapse over a longer period. Secondly, among the domains of the EE, only CC was found to be significantly related to relapse and warmth domains of EE can reduce risk of relapse. Currently, family psychoeducation appeared to be an effective treatment modality to reduce EE domains such as EOI (Pharoah, Mari, Rathbone, & Wong, 2010), CC

(Ma, Chien, & Bressington, 2018; Pharoah et al., 2010), and hostility (Pharoah et al., 2010). However, the treatment effect on global EE was equivocal (Sin et al., 2017). Results of the current study suggested that intervention focusing on reducing CC domains of EE might have more significant benefit to change relapse outcomes. Two recent systematic reviews found cognitive behavioural family intervention and compassion-focused therapy may be beneficial to the schizophrenic patients and their families, in which both of the interventions target on the cognitive reappraisal and emotional resilience to foster family climate and dynamic (Ma et al., 2020; Mui et al., 2019). These evidences confirmed the foci of family intervention with the purpose of reducing EE, specifically CC domains and enhancing sense of warmth. Though studies reported the nature of the relationship between caregiver and patients, few reported its effect on the EE-relapse relationship. Current study found parental HEE is a significant risk factor of relapse, it might be only an observational finding (Higgins et al., 2020). Further studies will be needed to explore in detail the role of nature of relationship between caregivers and patients on the link of EE and relapse. Finally, we found that a greater number of HEE families were detected in Western countries than the Eastern countries. An earlier review suggested Western culture encourages more direct expression and individuals tend to have higher emotional arousal and that might explain the difference of EE level between culture (Hooley, 2007). However, similar with the previous two review studies, we found culture was not a significant factor in moderating the relationship between HEE and relapse.

Differ from the earlier meta-analysis (Butzlaff & Hooley, 1998), length of condition was not found to be a significant moderator of the EE-relapse association. This is possible that more studies involving patients with earlier stages of condition have been conducted since the first review. Our results suggest that EE is an important contributor to relapse among patients with different stages of condition. Current study further explores other possible moderating factors including age, EE measures, RoB and publication years and none were found to be significant moderators. This highlighted the robustness of the relationship between HEE and relapse. The lack of significant impact of EE measures suggested that other valid EE measurements may also be sensitive in the study of EE and relapse.

The results of the current study should be interpreted with regard to the following limitations. Firstly, the operational definitions of relapse across studies differed widely between studies with five studies used rehospitalisation solely as a relapse indicator without clinical measurements. This may have contributed to the variation of results. Secondly, in order

to avoid double counting, only studies with the longest follow-up was included for studies with multiple reporting. Thirdly, due to different covariate adjustments across studies, crude OR was extracted from individual reports rather than adjusted OR (if reported) to pool the effect estimates. Finally, because of small sample sizes in some of the subgroup analyses ($k < 10$), the corresponding findings should be interpreted in caution.

Conclusion

High EE is a robust predictor of schizophrenic relapse, with more impact on early relapse than that on late relapse. Among the four domains of EE, critical comments seem to be a significant factor related to relapse and level of warmth may have a protective role. Results confirmed the foci of family intervention on reducing EE, specifically reducing critical comments and improving level of warmth.

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Conflict of interest

None

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